MULTI-REGIONAL CLINICAL TRIALS

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

ACHIEVING DIVERSITY, INCLUSION, AND EQUITY IN CLINICAL RESEARCH

Guidance Document

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

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

This work is dedicated to all the individuals who have volunteered to participate in clinical trials to advance knowledge and improve human health. This work is also dedicated to all the individuals who have been underserved and underrepresented in research, for whom science and society have failed.

Barbara E. Bierer
Sarah A. White
Hayat R. Ahmed
Laura G. Meloney

If it were not for the great variability among individuals, medicine might as well be a science and not an art.

Sir William Osler
Johns Hopkins School of Medicine
The Principles and Practice of Medicine, 1892

Author's Note

This work began in May 2017, at an MRCT Center Bioethics Collaborative, a neutral forum during which a number of clinical research stakeholders convened to discuss diversity in clinical trials. The attendees of that meeting, represented by a multi-stakeholder group of industry, academia, government, and patient advocacy, agreed that the participant population enrolled in a clinical trial ought to be representative of the general population at a minimum and, optimally, of the intended population for the intervention. If study populations are skewed, if they lack diversity, then the safety and efficacy, effectiveness, and value of medical interventions—the biological heterogeneity of treatment effect—cannot be adequately investigated and understood. Justice issues also influence diversity – or lack thereof – of study populations, with a fundamental unfairness perceived if specific populations are either disproportionately burdened, or unfairly excluded, from study enrollment. The attendees at that meeting agreed that, despite the understood necessity as a matter of science and ethics, underrepresentation of gender, sex, ethnic, and racial minorities in drug development, and in clinical research more generally, persists.

The extent of the problem, particularly for underrepresented and underserved populations, came into stark relief in the U.S. with the first publication of FDA Drug Trial Snapshots in January of 2015.[1] Drug Trial Snapshots reports on the demographics (sex, age, race, ethnicity) of patients who participated in the pivotal trials of either new molecular entities (NMEs) or Biologics License Applications (BLAs) that led to product approval in that year. The report is truly a "snapshot," dependent upon the vagaries of the drugs and biologics approved in one year by one regulatory agency. With that limitation, the publication from the Center for Drug Evaluation and Research, developed in part in response to 2012 Food and Drug Administration Safety and Innovation Act (FDASIA 907), revealed striking disparities in participation by sex and race. In 2015, of 45 novel drugs approved, and with over 105,000 enrolled participants, only 40% of patients were women, and strikingly only 5% were African American. However, over the two year time frame of 2015 and 2016, 67 products were approved with dramatic variation by therapeutic area: the percent Black or African-American patients included was less than 3% of

[1] U.S. Food and Drug Administration. 2015-2016 Drug Trials Snapshots Summary Report. Available at https://www.fda.gov/media/103160/download [Accessed 14 June 2020]

the total in trials of products for both cardiovascular diseases (2.50%) and oncology (2.74%) while 24.18% of participants were Black or African-American in psychiatric disorder trials.[2] Thus, racial diversity in clinical trial participation and drug development was possible, it just was not occurring and apparently not prioritized.

These stark and sobering observations led to a robust discussion at the Bioethics Collaborative: diverse representation is a principle of justice and of a just society, and our collective failure to achieve diversity is a solvable albeit difficult problem. Since that time, there have been numerous additional reports in both the scientific literature and the public press recounting the lack of diversity in clinical trials, across the spectrum of demographic dimensions of diversity: race, ethnicity, sex, gender, the elderly, the young, and genetics, as well as non-demographic variables such as comorbidities, polypharmacy, organ dysfunction, etc. Importantly, the impact of social determinants of health on health outcomes in clinical trials cannot be measured in the absence of validated methods for categorization, which have not yet been universally adopted.[3]

It should be understood that some dimensions of diversity (e.g., age, sex) represent biological differences, while others (e.g., race, ethnicity) represent social constructs, not fundamental biology. Race and ethnicity may, however, serve as surrogates, albeit inadequate and often flawed surrogates, for other factors such as genetic allelic frequencies, environmental factors, and social conditions, and analysis of study populations using those constructs can identify underrepresentation about which we as a society should be deeply concerned. The mission of health regulatory agencies is, in part, to protect the public health of its population—all its people, of every demographic—by ensuring the safety, efficacy, and security of drugs, biologics, vaccines, devices, and other products. Inclusion of all populations is necessary for reasons of justice, health equity, and trust.

Understanding the problem, and finding approaches to mitigate underrepresentation, requires focus and commitment, and a larger workgroup was formed in the fall of 2017 to address diversity, inclusion, and equity in clinical research. The group was comprised of representatives

[2] U.S. Food and Drug Administration. 2015-2016 Global Participation in Clinical Trials Report. Available at https://www.fda.gov/media/106725/download [Accessed 14 June 2020]. *Note*: the percent (number/total) of participants enrolled in the pivotal trials differed across the therapeutic areas: cardiovascular diseases 2.50% (1,415/92,329) , oncology 2.74% (211/7,480), and psychiatric disorders 24.18% (1,405/4,405).

[3] The absence of data on social determinants of health is a significant deficiency, foreclosing opportunities for correlative studies that may be meaningful and potentially more relevant than other factors.

from academia, industry, patients, participants, advocacy organizations, regulatory agencies, non-profit organizations, and others. The group has worked steadily, meeting monthly, over the last 2+ years, and it has grown accustomed to often uncomfortable and challenging, but always respectful, conversation.

While the problem seemed important and relevant over the last few years, it is today an imperative that is foundational to society and to medicine. The COVID-19 pandemic exposed great inequities in health: Black, Latinx, Pacific Islander and some vulnerable (e.g., homeless, incarcerated, aged, institutionalized) populations have been disproportionately affected by the SARS-CoV-2 virus, and the disease has greater severity and mortality among those populations. This disproportionate impact appears to be related to comorbidities (e.g., hypertension, diabetes, obesity), access to healthcare and prompt testing, inequities in healthcare delivery, immune compromise secondary to chronic stress and other factors, exposure risks (e.g., density of living quarters, dependence on public transportation, work requirements), and/or potential genetic differences, among other factors. The fact that we do not know the relative contribution of these underlying factors, and lack data addressing them, exposes the degree of the problems we face today.

In this time of a global pandemic crisis came yet another example of racism in the United States with the tragic and painful death of George Floyd, and that death followed Ahmaud Arbery, Breonna Taylor, and countless others before them. In the U.S. and internationally, the world is rising to decry inequalities in power, opportunity, access, and, importantly, health.

This moment is a—long delayed—call to action. Eliminating racism and racial inequalities begins with eliminating disparities in health, and that necessarily demands deliberate and purposeful inclusion in health research that itself will help lead to equitable access and outcomes. This document addresses one part of that manifest inequity. To address that inequity successfully requires inclusion of diverse populations in research to advance the science - science that can then help create and implement data-driven, impactful solutions.

While we would like to believe that the work presented in this document is timely and relevant, in fact it is long overdue, and it is only a beginning. We appreciate that. We also know that we must start somewhere. The real work lies ahead, and for that, every member of the clinical research enterprise must commit, engage, and respond for real change to be lasting and

impactful. We must value not only the imperative to understand biological differences but also the need to improve the health of all populations, eliminate disparities, and advance health equity.

Barbara E. Bierer, MD
June 15, 2020

Citation Statement

We invite the international research community to use and cite the MRCT Center Guidance Document *Achieving Diversity, Inclusion, and Equity in Clinical Research* and the accompanying *Toolkit*, which can be freely quoted and used to promote the values, principles and content articulated therein. Any use or citation, however, must expressly and prominently indicate the source documents and its MRCT Center authorship and provenance.

The MRCT Center allows the use and adaptation of the associated tools as long as the user gives prominent credit and attribution to MRCT Center Guidance Document as the source, and as long as adaptation of tools and their use is consistent with the values and principles set forth in the MRCT Center Guidance Document. If adapted tools are published in any way, the MRCT Center requires that as a condition of use, the user promptly provide a copy to MRCT Center (mrct@bwh.harvard.edu) so that we may understand how the tools have been used, adapted and refined, to inform our future efforts on these issues.

Suggested citation:

Bierer B.E., White S.A., Meloney L.G., Ahmed H.R., Strauss D.H., Clark L.T., (2020) *Achieving Diversity, Inclusion, and Equity in Clinical Research* Version 1.0. Cambridge and Boston, MA: Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center). Retrieved from: https://mrctcenter.org/diversity-in-clinical-trials/

Acknowledgements

When the MRCT Center team began to address the challenges of diversity, inclusion, and equity in clinical research, we knew that it would require considerable research, difficult conversations, thoughtful analysis, practical thinking, and time. The process of writing this Guidance Document and Toolkit has been challenging. With time, it became important to us to help clinical research stakeholders advance diversity and inclusion not only in clinical research but also for health equity.

None of this work would have been possible without the thoughts, opinions, and practical experience of the Diversity Workgroup. More than two years of group calls, plus countless individual calls and emails helped shape our thinking, the document, the specific examples, and tools. We are ever grateful for the Workgroup's experience and contributions.

This project began by active collaboration with John Whyte and Junyang Wang, with the support of Janet Woodcock, Director, FDA Center for Drug Evaluation and Research (CDER). The work was completed only through the close collaboration, guidance, and friendship of RADM Richardae Araojo, Associate Commissioner for Minority Health and Director of the Office of Minority Health and Health Equity, FDA Office of the Commissioner, and Milena Lolic, Lead Medical Officer, Professional Affairs and Stakeholder Engagement, FDA CDER Office of the Center Director. It is their collective vision and advice that gave us the courage to drive this initiative forward.

Logistically managing the creation of such a large guidance document with figures, tables, cases, and tools was no small task. Tracking the development and progress of the Guidance Document and Toolkit would never have been possible without the expert project management and organizational skils of Carmen Aldinger. We appreciate Carmen's calm approach and continuous reminders to keep us on track.

Jennifer Ewing, our Senior Communications Specialist, is responsible for the layout and design, and for bringing a certain respectfulness and consideration to the presentation itself. She has our enduring appreciation not only for her creativity, but equally for tolerating our endless

suggestions and changes, many so trivial that the common mortal would be ever so irritated, with equanimity, humor, and grace.

We were and are consistently impressed by Joshua Smith-Sreen, our undergraduate and then graduate student researcher who imagined and created practical tools from pages of dense content. Josh brought energy, constant optimism, and dedication to the work of the MRCT Center, all of which helped move the document toward completion.

We are grateful to William Tap (Memorial Sloan Kettering Cancer Center), Matthew Rotelli (Eli Lilly and Company), and Maria De Leon (Parkinson's Foundation) – the first three reviewers of this Guidance Document outside of the Diversity Workgroup—for their helpful comments that guided the further development of this Guidance.

There are a few Workgroup members whose thoughts and comments particularly impacted the thinking of this document. Thanks to Patrick Cullinan (Takeda, currently BlueBird Bio) – we will always think of Figure 7 as "Paddy's figure;" Steve Snapinn (Seattle-Quilcene Biostatistics) – no one can explain complex data analytic concepts more clearly; Roberto Lewis (Columbia University) – for continuously reminding us that race and ethnicity are social constructs and to focus on both equity and biology; Theresa Devins and Anne-Marie Inglis—for keeping us grounded in practical deliverables; and Jessica Scott (Takeda) – for always considering the patient and participant perspective and the importance of engagement throughout the product development lifecycle.

Thanks to Mark Barnes (Faculty Co-Director of the MRCT Center and Partner at Ropes & Gray) for his continuous strategic advice, support, and enthusiasm for the work of the MRCT Center. We are grateful for the trust and support of our Executive and Steering Committee members who listened to and challenged us to go further for more than two years while patiently waiting for us to develop this Guidance Document. Their individual and collective confidence in the MRCT Center makes a difference. We are thankful to our External Advisory Board for the strategic direction and always positioning our work in the global setting. And to the MRCT Center's team and their never-wavering patience and continuous support of this project helped carry us to the end.

Lastly, we are grateful to those reading this document – as investigators, scientists, regulators, bioethicists, team members—and, most particularly, patients, participants, and their families. We appreciate those who do and will think critically about what is missing in the document and ask you to help us make it better. We appreciate those who do and will think critically about the work to be done now and in the future. But the real work of change is done year by year, month by month, and day by day, by all of us, by each of us, and for that we thank you.

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.[4] 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.[5] 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.[6] 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.[7] 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,

[4] Knepper TC, McLeod HL. When will clinical trials finally reflect diversity?. Nature 2018 May 557,157-159.
[5] Modeling, other simulation techniques, and newer analytic approaches may help approximate understanding of treatment and other outcomes.
[6] 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.
[7] 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.

combining studies using shared individual participant data, and studies using real world data 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,[8] 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.

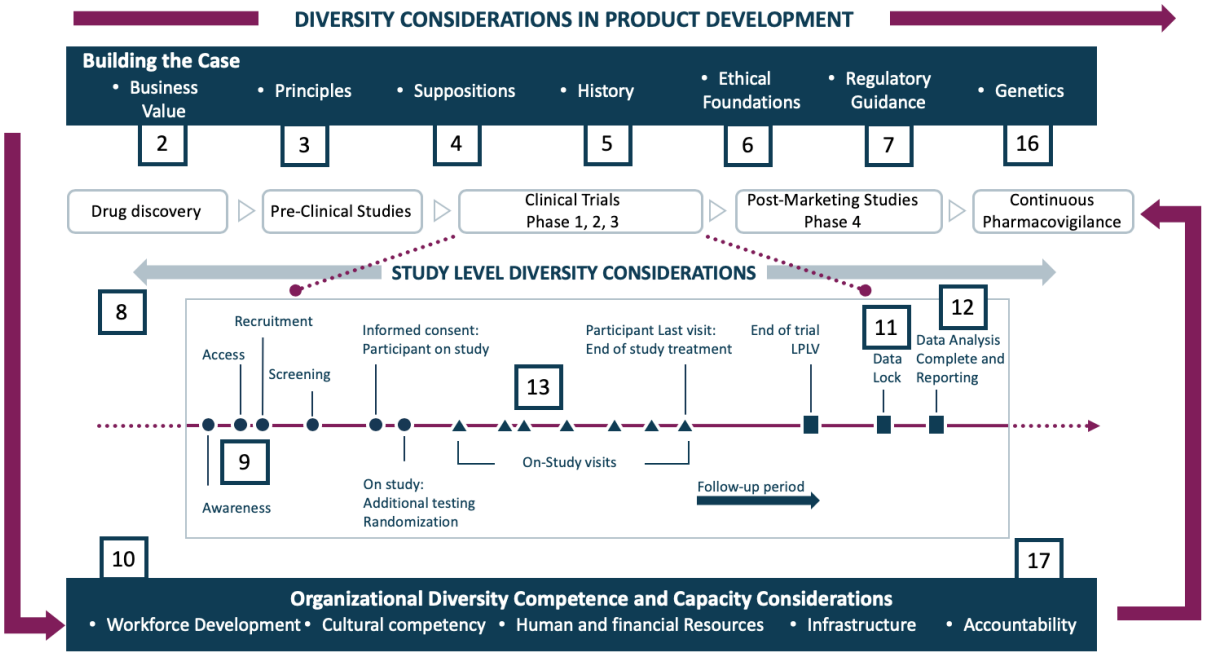
In addition to the biological importance of heterogeneity of treatment effect, there are reasons of health equity and social impact to support and promote appropriate inclusion of diverse populations in clinical research. As an important ethical principle, justice and fairness in distribution of the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

[8] 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.[9,10,11] 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



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

[10] 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.

[11] 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 circules. (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.

Table of Contents

List of Figures

List of Tables

Preface

Members, Writers, and Reviewers

A 50+-member international multi-stakeholder workgroup convened by the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard University (MRCT Center) developed this Guidance Document and accompanying *Toolkit*. While every member contributed to the development of the *Diversity Framework*, the leadership of the MRCT Center is responsible for the final content.

> *The views and findings expressed in this document are those of the authors and do not imply endorsement or reflect the views or policies of the U.S. Food and Drug Administration or the affiliated organization or entity of any member who contributed to this work. Individuals have served in their individual capacity.*

Leadership team

- RADM Richardae Araojo, U.S. Food and Drug Administration (as of August 2018)
- Barbara E. Bierer, MD, MRCT Center
- Luther T. Clark, MD, Merck & Co., Inc.
- Milena Lolic, MD, U.S. Food and Drug Administration (as of August 2019)
- David H. Strauss, MD, Columbia University
- Junyang Wang, MSc, U.S. Food and Drug Administration (until August 2019)
- Sarah White, MRCT Center
- John Whyte, MD, MPH, U.S. Food and Drug Administration (until August 2018)

MRCT Center staff:

- Carmen Aldinger, Administrative & Training Manager
- Hayat Ahmed, Project Manager
- Laura Meloney, Program Manager
- Joshua Smith-Sreen, Student Researcher

Principal writers

- Barbara E. Bierer, MRCT Center
- Sarah White, MRCT Center
- Laura Meloney, MRCT Center
- Hayat Ahmed, MRCT Center
- David H. Strauss, Columbia University
- Luther Clark, Merck & Co., Inc.

Workgroup members

Name	**Organization**
Maria Apostolaros	Pharmaceutical Research and Manufacturers of America (PhRMA)
Abhijit Bapat*	Novartis
Stacey Bledsoe*	Eli Lilly and Company
Shari Bodnoff*	Novartis
Racquel Bruton	Biogen
Elizabeth Cahn	Cancer Connection
Li Chen	Amgen
Patrick Cullinan	Takeda, currently BlueBird Bio
Liza Dawson*	National Institutes of Health (NIH)
Maria De Leon*	Parkinson's Foundation
Theresa Devins	Boehringer Ingelheim, currently Regeneron Pharmaceuticals
Anthony Edmonds	Takeda
Rhonda Facile	Clinical Data Interchange Standards Consortium (CDISC)
Rachael Fones	IQVIA
Laura Gordon*	Institute for Advanced Clinical Trials for Children (iACT)
Anya Harry	GlaxoSmithKline (GSK)

Melissa Heidelberg	Genentech/A Member of the Roche Group
Quita Highsmith	Genentech/A Member of the Roche Group
Sharareh Hosseinzadeh	Novartis
Lloryn Hubbard*	Genentech/A Member of the Roche Group
Anne Marie Inglis*	GlaxoSmithKline (GSK), currently Mallinckrodt Pharmaceuticals
Aarthi B. Iyer*	Kinetiq, now Advarra
Becky Johnson*	IQVIA
Tesheia Johnson	Yale School of Medicine
Jonathan Jackson*	Massachusetts General Hospital
Marcia Levenstein	Vivli
Roberto Lewis	Columbia University
Eldrin Lewis	Brigham and Women's Hospital, currently Stanford University
Jianchang Lin*	Takeda
Erin Muhlbradt	National Cancer Institute (NCI)
Isabela Niculae *	Biogen
Latha Palaniappan	Stanford University
Claude Petit	Boehringer Ingelheim
Claire Pigula*	Biogen
Melissa Poindexter*	Advances in Health
Nicole Richie	Genentech/ A Member of the Roche Group
Bryant (Abel) Riera*	Population Council
Suzanne M. Rivera	Case Western Reserve University
Frank W. Rockhold	Duke University
Ricardo Rojo*	Pfizer
Rosanne Rotondo*	Novartis
Fabian Sandoval	Emerson Clinical Research Institute

Richard Sax*	IQVIA
Hollie Schmidt	Accelerated Cure Project for Multiple Sclerosis
Karlin Schroeder	Parkinson's Foundation
Mary Scroggins*	Pinkie Hugs
Jessica Scott*	Takeda
Lana Skirboll	Sanofi
Steven Snapinn	Seattle-Quilcene Biostatistics
Stacey Springs*	Harvard Medical School
Sara Tadesse-Bell	Genentech/ A Member of the Roche Group
Ann Taylor*	Columbia University
Paul Underwood	Boston Scientific
Junyang Wang*	Food and Drug Administration (FDA)
Robert Winn*	University of Illinois
Gerren Wilson*	Genentech/ A Member of the Roche Group
Crispin Woolston	Sanofi
Honghui Zhou*	Johnson & Johnson

*involvement limited in time

Additional reviewers

- Mark Barnes, Ropes & Gray and MRCT Center
- Maria DeLeon, Parkinson's Foundation
- David Hawks, National Council of Asian Pacific Islander Physicians and Alliance of Multicultural Physicians
- James H. Powell, Strategic Medical Associates
- Matthew Rotelli, Eli Lilly and Company
- William Tap, Memorial Sloan Kettering Cancer Center

Roadmap

This is a comprehensive and somewhat complex document that benefits from explanation of its component parts (the "Roadmap"). **Part A** begins with the **objectives** (Chapter 1) followed by **the case for diverse representation and inclusion** (Chapter 2)**,** establishes its importance to biological, scientific, social, ethical, and financial priorities, and explains the **business value** for clinical trial sponsors, healthcare institutions, research sites, payers, and other stakeholders. We identify a set of overarching **principles** (Chapter 3), followed by important **suppositions** (Chapter 4) that we believe guide considerations of representativeness in clinical research. These **principles** and **suppositions** lay the foundation for our further observations and suggestions. They are intentionally broad, and their translation into action requires further specificity that is discussed later.

In **Part B** we include a brief review of the **history, scope, and background** (Chapter 5) for inclusivity before presenting the **application of ethical principles** to diverse representation (Chapter 6), followed by a review of existing **regulations and guidance**[12] (Chapter 7) in the U.S. and in selected global regulatory agencies, appreciating that certain issues (e.g., race, ethnicity) have different meanings and are subject to different considerations depending on region.

Part C of the document focuses on **broadening engagement** and calls out the role of **patients, caregivers, communities, and patient advocacy organizations** (Chapter 8) as we believe that active partnership with these individuals and communities is essential to improve the evidence base for outcomes that are relevant and meaningful to patients and the public, and that are respectful of different cultures and communities. We recognize the importance of patient and participant, caregiver, health care provider, and community **awareness, knowledge, and access** (Chapter 9). We highlight the need for training of the current workforce and the importance of long-term commitment to the development of a **diverse Workforce** (Chapter 10).

[12] Some important examples only are included, last reviewed February 24, 2020.

In **Part D** we review certain quantitative scientific issues, including issues of **data collection, reporting, data analysis** (Chapters 11 and 12), and the scientific analysis of variability of benefits and risks of treatment.

In **Part E** we discuss **study design and implementation** (Chapter 13) and present many of the apparent **impediments,** practical **barriers** and constraints to inclusion of a diverse population and suggest recommendations and **solutions** to many as well as the **role and responsibilities of Institutional Review Boards (IRBs)/Research Ethics Committees (RECs)** in conducting ethical review and oversight (Chapter 14). We include a reserved chapter on **special populations** (Chapter 15) that we plan to expand in the near future.

In **Part F**, the document then moves to a discussion of the implications of **genetics and diversity in clinical research** (Chapter 16). We also address **stakeholder** r**oles, responsibilities and accountability in promoting diversity** (Chapter 17) **–** the ways that each stakeholder group may impact change. We refer to some **Case Studies** throughout the document including examples of successful approaches, each explained further in the *Toolkit*. We end with thoughts of **future directions and conclusions** (Chapter 18) including the role of real world evidence and system reconsiderations.

A list of **abbreviations** (Appendix 1) is found in **Part G**, as is a **glossary** (Appendix 2) to define the list of terms as used in this document. We realize that many terms have various definitions and meaning, and we therefore sought to define the terms as used here. We also include a separate page on **terminology of race and ethnicity used in this document** (Appendix 3). We appreciate that issues of diversity and inclusion in research are complex and evolving, and that words and context matter. We have done our best throughout this document to be thoughtful in our discussion, but we realize that misinterpretations are not only possible but inevitable. Nothing here is meant to be prescriptive; our comments and recommendations should be interpreted and applied based on context-specific analyses. We would do a disservice to the complexity of these issues, however, by ignoring them.

We realize that clinical science is only at the beginning of creating a successful approach to the understanding of biological heterogeneity on the one hand, and of achieving health equity[13] on the other. We support the academic pursuit of population and outcomes science to understand both biological heterogeneity and the depth and extent of the health equity challenge that, collectively, we need to correct. We understand this work is part of the beginning of a long-term, cooperative effort on behalf of all stakeholders, and we anticipate updating this Diversity Framework from time to time. We welcome feedback, contributions, case studies, and success stories (email: mrct@bwh.harvard.edu), and we will periodically revise these work products. Additional resources may be found in the *Toolkit* that accompanies this document.

[13] The World Health Organization defines health equity as "the absence of avoidable, unfair, or remediable differences among groups of people, whether those groups are defined socially, economically, demographically or geographically or by other means of stratification. "Health equity" or "equity in health" implies that ideally everyone should have a fair opportunity to attain their full health potential and that no one should be disadvantaged from achieving this potential." See https://www.who.int/topics/health_equity/en/ [Accessed 27 May 2020]

Part A – Building the Case

1. Objectives

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) Diversity Workgroup was formed in February 2018 to clarify the meaning and advance the goals of diverse representation of participants in clinical research. In addition, the workgroup aimed to substantiate and qualify the value of diversity to the science of biological variability, health care, and social justice, and explore why diverse representation has not increased despite numerous calls to action.

The workgroup met together by conference call monthly, in occasional small meetings, and in small task groups to examine component issues and questions. About 25 members of the workgroup met in person in November 2019 at Harvard University to review the draft document, discuss the work, identify gaps, and address the approaches and solutions suggested.

The workgroup endeavored to identify and analyze barriers that limit diverse participation, and to develop and disseminate resources such as guidance materials, tactical strategies, and tools to advance required changes to conceptual, organizational, and operational challenges. In the service of science, equity, and public health, we call on all stakeholders to do more, to address the inequity, and to advance the understanding of biological diversity in medicine.

The MRCT Center's *Achieving Diversity, Inclusion, and Equity in Clinical Research* (the *"Diversity Framework"*) outlines a principled, multi-stakeholder approach to optimize the inclusion of diverse populations in clinical research. The *Diversity Framework* includes this *Guidance Document* as well as the accompanying *Toolkit,* and those tools that have been prepared to date are available here. The *Toolkit* is a dynamic resource and will be periodically updated and expanded. Please send additional suggestions or examples to mrct@bwh.harvard.edu; we will communicate the availability of new tools through our periodic newsletter (sign up here: https://tinyurl.com/yd6ulgnj), LinkedIn and Twitter.

2. The Case for Diversity in Clinical Research

Figure 1: Case for diversity topics

The MRCT Center convened a multi-stakeholder working group to examine current efforts to increase diverse representation and promote inclusion in clinical research,[14] identify existing impediments to achieve increased diversity, and develop and disseminate practical tools to enable progress. We believe this work has important implications for clinical research, the process by which new therapeutic agents and devices are tested and then studied in the post-marketing environment, and ultimately, for the health of the public. Figure 1 presents the topics addressed in this chapter.

[14] *Clinical research* is the study of people, either through direct interaction or through the collection and analysis of data, blood, tissues, or other samples, to advance medical knowledge. A *clinical trial* involves research participants and follows a pre-defined plan or protocol to evaluate the effects of a medical or behavioral intervention on health outcomes. Clinical research includes clinical trials as well as other forms of research with human data and specimens. Please see Glossary for definitions.

Historically, clinical research focused on product development has been often criticized for enrolling largely homogeneous populations that are not representative of the populations anticipated to use the product under intended circumstances. Why, and to what extent, should study populations in clinical research represent the diversity of U.S. and global populations? First, it is generally acknowledged that clinical research in which study populations mirror the characteristics of the population impacted by a particular illness or condition can better serve individuals who subsequently use an intervention or approved therapeutic agent.[15] Variations in treatment outcome and in disease biology among subgroups, when they exist, have the possibility of being identified when those subgroups are included in clinical research;[16] in their absence, those subgroups may be misinformed by or distrust the resulting evidence base,[17] and significant opportunities to identify unique reactions or efficacy can be lost. Second, ethical (social justice) imperatives, and specifically fairness in the distribution of the opportunities and potential benefits (and burdens) of the health research, drive expectations for diverse inclusion in clinical research.[18,19] Nowhere has this been more aptly or dramatically demonstrated than during the COVID-19 pandemic. Third, analyses of group differences in safety and efficacy among diverse populations can promote identification of underlying biological factors and socially relevant factors that affect health (broadly speaking, the "social determinants of health"). For all these reasons, improved representation of diverse or under-researched

[15] Knepper TC, McLeod HL. When will clinical trials finally reflect diversity?. Nature 2018 May 557,157-159.
[16] Modeling, other simulation techniques, and newer analytic approaches may help approximate understanding of treatment and other outcomes.
[17] 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.
[18] Caplan A, Friesen P. Health disparities and clinical trial recruitment: Is there a duty to tweet?. PLoS biology. 2017 Mar 1;15(3):e2002040.
[19] 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.

populations is necessary in U.S. and global, government-supported and regulated research, and in both industry and academia-sponsored studies.[20,21]

Despite the evident value of diversity and inclusion, an extensive literature search reveals that efforts to fulfill the scientific goals of diversity—namely, the identification of variability in treatment response and safety across subgroups—have not been successful.[22] The challenges to the inclusion of diverse populations take many forms, with operational, commercial, and cultural dimensions.[23] It is true that as contemporary clinical research is often multi-centered and international in nature (and with a decreasing U.S.-based recruitment across the pharmaceutical industry's clinical trials), additional diversity barriers exist across sites, countries and regions.[24] Moreover, a fundamental scientific impediment derives from the fact that clinical trials rarely have the necessary numbers of enrolled subjects to permit definitive subgroup analyses.[25]

Other factors affect the perceived value of increasing diversity in clinical research. In an era of genomic discovery, self-reported racial, ethnic, and other demographic distinctions are poor approximations of genetic and biological determinants of health and treatment response.[26] Yet race, ethnicity and other characteristics can serve as surrogates— often inadequate and flawed

[20] FDASIA Section 907: Inclusion of Demographic Subgroups in Clinical Trials. https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm389100.htm [Accessed 27 May 2020]

[21] Center for Drug Evaluation and Research. (n.d.). Enhancing the Diversity of Clinical Trial Populations - Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry. June 2019. Retrieved from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial [Accessed 27 May 2020]

[22] Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington RA, Califf RM, Schulman KA. Ethical and scientific implications of the globalization of clinical research. N Engl J Med. 2009 Feb 19;360:816.

[23] 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. American journal of public health. 2014 Feb;104(2):e16-31.

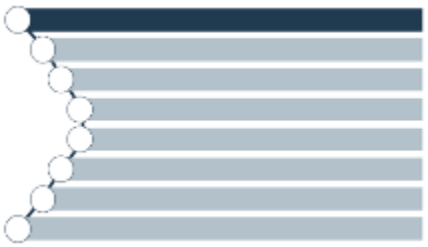
[24] Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington RA, Califf RM, Schulman KA. Ethical and scientific implications of the globalization of clinical research. N Engl J Med. 2009 Feb 19;360:816.

[25] 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.

[26] Mersha TB, Abebe T. Self-reported race/ethnicity in the age of genomic research: its potential impact on understanding health disparities. Human genomics. 2015 Dec 1;9(1):1.

surrogates—for social determinants of health (see Chapter 3 "Basic Principles"); they are linked to cultural factors, education, socioeconomic status, geography, and pathways to care, each of which influences disease characteristics and treatment outcome[27] in ways that are incompletely understood.

Given the considerations that support or detract from a case for increasing diversity, a more complete discussion of its aims and implications is presented in the remainder of this section.



2.1 Biological variability and society

In the U.S. and abroad, regulatory approvals for investigational products[28] are based on carefully designed, and typically blinded and randomized, clinical trials.[29] Drug, biologic, and device trials are then followed by post-approval research that includes both interventional and observational studies. Ideally, research yields generalizable knowledge pertinent to the population that has that disease or condition, or that will use the product or intervention. As product safety and effectiveness can vary depending on demographic factors (e.g., an individual's sex, race, ethnicity, age, genetics) and non-demographic factors (e.g., comorbidities, other medications, social determinants of health, diet, climate), clinical trials should also provide information on the use of therapeutic agents within identified subgroups. However, often there are insufficient data in advance of a trial to know whether differences in either safety or efficacy by subgroup warrant investigation. Further, even in cases where relevant subpopulations are represented in clinical trials, studies are rarely powered to permit an informative analysis of treatment outcome by subgroup.

[27] Singh GK, Daus GP, Allender M, Ramey CT, Martin EK, Perry C, De Los Reyes AA, Vedamuthu IP. Social determinants of health in the United States: addressing major health inequality trends for the nation, 1935-2016. International Journal of MCH and AIDS. 2017;6(2):139.

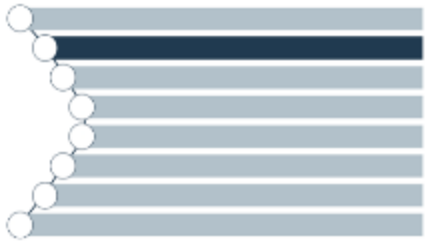
[28] Here, the term "product(s)" implies drugs, biological products, devices, vaccines, and other approaches (e.g., gene therapy) regulated by national regulatory health authorities. The descriptor "investigational" (e.g., "investigational product") implies that the product has not been approved for the indication.

[29] For the remainder of the document, the term "clinical trials" is used to refer not simply to research that supports regulatory approval, but any clinical research that involves the prospective assignment of individuals who volunteer to test the safety and effectiveness of a investigational or approved drug, biologic, vaccine, device, therapy, or intervention. Hereinafter, the term "drug" or "intervention" is meant to include these modalities.

Clinical trials cannot reasonably and practicably be designed to yield statistically conclusive results for all subgroup comparisons. To do so would be to increase the sample size and/or extend the time course for study completion, thus imposing potentially tremendous transaction costs on the research enterprise that could delay treatments and do more harm than good. While inclusion that would allow accurate subgroup analysis is potentially possible for large subgroups (e.g., sex, region), it cannot be done for all possible subgroups and subpopulations.

If obtaining statistically conclusive results is challenging, can another analytic framework be informative? Only through the collection of common data variables and their analyses will there be any understanding of heterogeneity of effect (see Chapter 11 "Data Variables and Collection" and Chapter 12 "Approach to Data Analysis"). Further, in some cases, a judicious *overrepresentation* of selected subgroups based on the populations at risk, existing data from earlier trials, mechanism of action, pharmacodynamics, pharmacokinetics, or pharmacogenetics, post-approval data collection, and/or real world evidence may be appropriate for understanding and elucidation of heterogeneity of treatment effect, or lack thereof.

In all, this call for diversity in the clinical research enterprise focuses attention on a number of variables, from those that are directly biologically relevant, others that are potential mediators of latent biological processes, and some for which the significance is unknown. Those planning and implementing clinical research must think through whether and how both demographic and non-demographic variables may influence treatment outcome and affect public health.



2.2 Justice and equity in health care research

The failure to achieve meaningful diversity in clinical research has important ethical and social implications. The Belmont Report[30] cited "moral requirements that there be

[30] 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.

fair procedures and outcomes in the selection of research subjects," and this notion of justice became a foundational ethical principle guiding decisions about participant inclusion in clinical trials. The Belmont Report also recognized that it was unjust to "offer potentially beneficial research only to some patients who are in their favor." This concept of fairness as access to the potential benefits of research[31] is relevant at both the individual level and population level. At the individual level, inclusion in clinical trials potentially affords access to investigational therapies and, often, advanced medical interventions not available outside the research context. At the group level, and for subgroups that have been under-studied whether systematically or incidentally, it is arguably the case that the evidence base relevant to their care and treatment is lacking. This is the core of current health equity concerns about diversity in clinical trials and is relevant to the historical indifference to racial and ethnic minorities as well as women's health,[32,33] pediatrics,[34,35] adolescent and young adults,[36,37,38] and the elderly.

[31] Note that there is no assumption that participation in a clinical trial is always a benefit, including in randomized trials. In clinical trials, there is clinical equipoise; there is no expectation that the experimental treatment offers a benefit relative to the control treatment. An equally valid argument is that clinical trial participants sacrifice in order to help future patients, including incurring a risk of harm in the absence of known benefit.

[32] Chen A, Wright H, Itana H, Elahi M, Igun A, Soon G, Pariser AR, Fadiran EO. Representation of women and minorities in clinical trials for new molecular entities and original therapeutic biologics approved by FDA CDER from 2013 to 2015. Journal of Women's Health. 2018 Apr 1;27(4):418-29.

[33] Vitale C, Fini M, Spoletini I, Lainscak M, Seferovic P, Rosano GM. Under-representation of elderly and women in clinical trials. International journal of cardiology. 2017 Apr 1;232:216-21.

[34] Aristizabal P, Singer J, Cooper R, Wells KJ, Nodora J, Milburn M, Gahagan S, Schiff DE, Martinez ME. Participation in pediatric oncology research protocols: racial/ethnic, language and age-based disparities. Pediatric blood & cancer. 2015 Aug;62(8):1337-44.

[35] Bourgeois FT, Olson KL, Ioannidis JP, Mandl KD. Association between pediatric clinical trials and global burden of disease. Pediatrics. 2014 Jan 1;133(1):78-87.

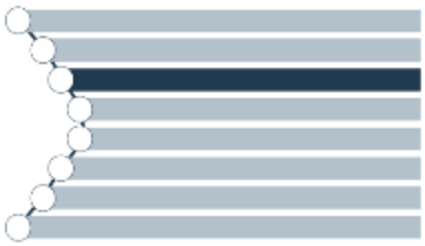
[36] Mason MJ, Luckey B. Young adults in alcohol-other drug treatment: An understudied population. Alcoholism Treatment Quarterly. 2003 May 5;21(1):17-32.

[37] Zhang RQ, Shi Z, Chen H, Chung NY, Yin Z, Li KK, Chan DT, Poon WS, Wu J, Zhou L, Chan AK. Biomarker-based prognostic stratification of young adult glioblastoma. Oncotarget. 2016 Jan 26;7(4):5030.

[38] Nahata L, Chen D, Moravek MB, Quinn GP, Sutter ME, Taylor J, Tishelman AC, Gomez-Lobo V. Understudied and under-reported: fertility issues in transgender youth—a narrative review. The Journal of pediatrics. 2019 Feb 1;205:265-71.

[39,40,41,42,43] Finally, public opinion, and specifically the trust of members of typically underrepresented and underserved groups, are compromised when studies are not appropriately inclusive. Treatments that result from these studies – especially those that have major impact on public health – will predictably have less positive impact if the populations that could benefit do not trust in the evidence of efficacy and safety.

The ultimate goal of diversity is an improved and personalized evidence base that addresses differences of biological and medical relevance. A secondary outcome is wider access to the potential benefits of inclusion in clinical trials, an especially important issue for conditions of unmet medical need in which access to clinical research may constitute the only access to potential treatments. Identification of differences relevant to subpopulations likely to be differentially affected requires their inclusion in a deliberate manner and the appropriate prioritization of the goals of diversity within the broader clinical trials agenda.



2.3 Defining diversity

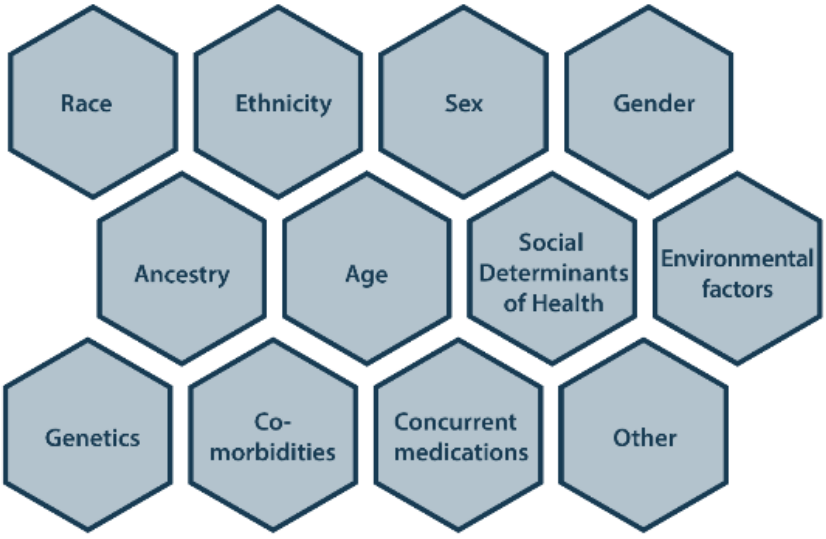
In this work, we have chosen an expansive definition of "diversity," one that is broad, inclusive of those factors that are invariant or unmodifiable, also termed "demographic" (e.g., sex, race, age, genetics), those that are potentially dynamic and may change or be modified over time, also termed "non-demographic" (e.g., comorbidities, organ dysfunction, concurrent medications, environmental factors, compliance

[39] Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. Journal of clinical oncology. 2005 May 1;23(13):3112-24.
[40] Mangoni AA, Jansen PA, Jackson SH. Under-representation of older adults in pharmacokinetic and pharmacodynamic studies: a solvable problem?. Expert review of clinical pharmacology. 2013 Jan 1;6(1):35-9.
[41] Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. Journal of general internal medicine. 2011 Jul 1;26(7):783-90.
[42] Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: known problem, little progress. Journal of Clinical Oncology. 2012 Apr 30;30(17):2036-8.
[43] BrintzenhofeSzoc K, Krok-Schoen JL, Canin B, Parker I, MacKenzie AR, Koll T, Vankina R, Hsu CD, Jang B, Pan K, Lund JL. The underreporting of phase III chemo-therapeutic clinical trial data of older patients with cancer: A systematic review. Journal of Geriatric Oncology. 2020 Jan 10.

[see Figure 2]). Among non-demographic factors are those that are historically, socially, and culturally determined. Diversity includes sexual and gender minorities[44] and social determinants of health (e.g., education, economic status, family size [see Figure 2]).

Each of these may be important in different circumstances depending upon the disease or condition, the population at risk, and the research question. Diversity is context-specific and the approach to and importance of diversity demands a context-specific analysis. Further complicating any attribution of a result to the outcome, different dimensions of diversity are often interdependent and interrelated (e.g., weight and physical activity, age and bone density, etc.); collinearity may impact a regression analysis intended to identify additional—but not independent—important variables.

Figure 2: Diversity exists across many dimensions



[44] In 2019, the definition of "sexual and gender minority" (SGM) populations was updated by the U.S. National Institutes of Health (NIH): "SGM populations include, but are not limited to, individuals who identify as lesbian, gay, bisexual, asexual, transgender, two-spirit, queer, and/or intersex. Individuals with same-sex or -gender attractions or behaviors and those with a difference in sex development are also included. These populations also encompass those who do not self-identify with one of these terms but whose sexual orientation, gender identity or expression, or reproductive development is characterized by non-binary constructs of sexual orientation, gender, and/or sex." From Sexual and Gender Minority Populations in NIH-Supported Research. Notice number NOT-OD-19-139, Release date August 28, 2019. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-139.html. [Accessed 27 May 2020.]

In this guidance, we draw upon terms and concepts first codified by the International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E5(R1) and shown in Figure 3.[45] ICH adopted the term "ethnic factors," to represent:

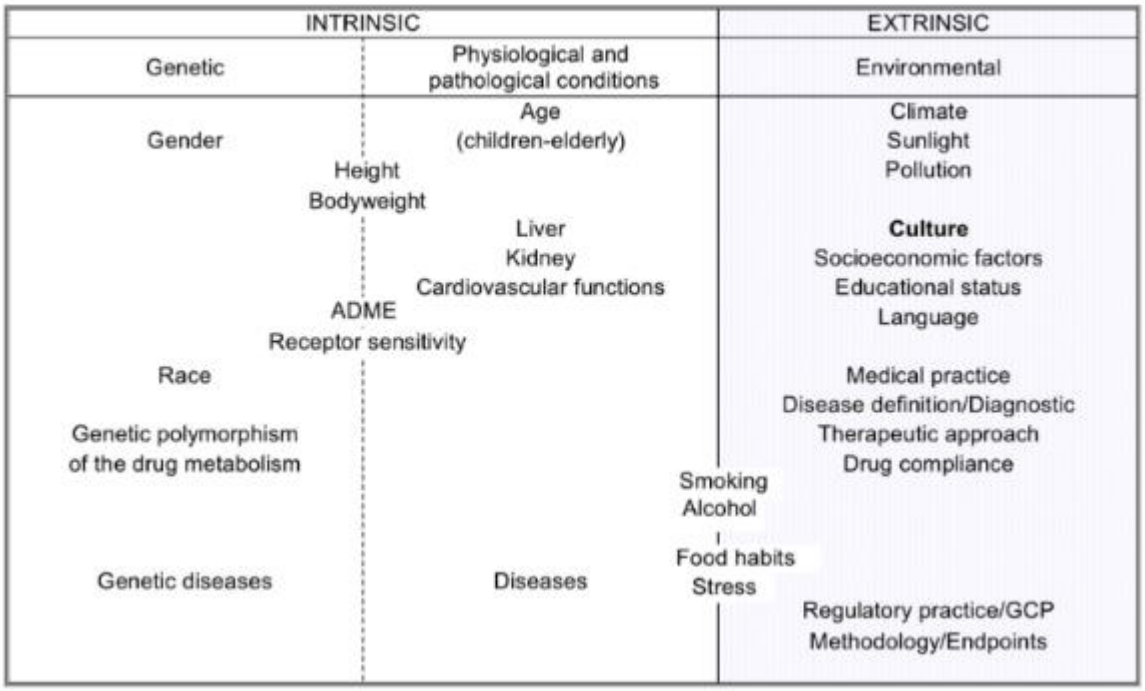
> …factors relating to races or large populations grouped according to common traits and customs. Note that this definition gives ethnicity, by virtue of its cultural as well as genetic implications, a broader meaning than racial. Ethnic factors may be classified as either intrinsic or extrinsic.[46]

[45] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline. Ethnic factors in the acceptability of foreign clinical data E5(R1). 5 February 1998. Available at: https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf [Accessed 2 January 2020.]

[46] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline. Ethnic factors in the acceptability of foreign clinical data E5(R1). 5 February 1998. Available at: https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf [Accessed 2 January 2020.].

Figure 3: ICH E5(R1) intrinsic and extrinsic factors

Classification of intrinsic and extrinsic ethnic factors



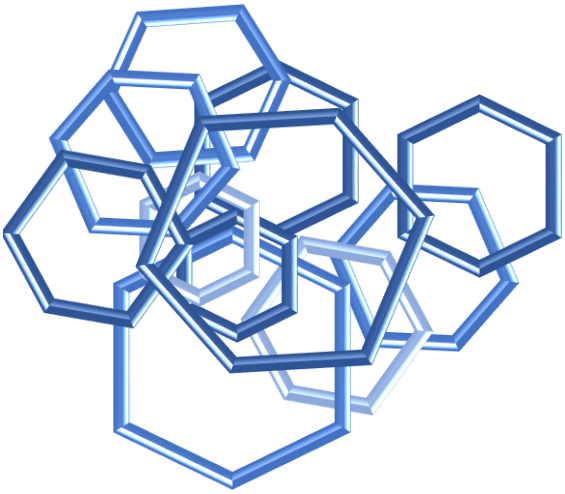
Reproduced from ICH E5(R1)[47]

The ICH E5(R1) guideline addressed the potential impact and consideration of ethnic factors upon a medicine's effect and recommended a framework for evaluation.[48] As the terms "ethnic" and "ethnicity" have varying connotations depending upon the setting, we use the term *diversity* to include the many "ethnic factors" described by ICH.

[47] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline. Ethnic factors in the acceptability of foreign clinical data E5(R1). 5 February 1998. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E5_R1/Step4/E5_R1__Guideline.pdf [Accessed 18 August 2019.]

[48] Guideline IH. Ethnic factors in the acceptability of foreign clinical data E5 (R1). InInternational Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use 1998 Feb 5;4.

Figure 4: Dimensions of diversity are not independent variables



It is important to appreciate that any individual may be characterized along multiple dimensions of "diversity," any of which—or many or all of which—may contribute directly or indirectly to treatment outcome. Further, dimensions of diversity are not independent variables but may influence one another (see Figure 4). In other words, a woman who is Black[49] may have a different disease prognosis, treatment response, or experience than a man who is Black or a woman who is White,[50] and these interdependencies expand with and complicate each dimension of diversity. In other words, a homosexual woman who is Black may also have a different disease prognosis, treatment response, or experience than a heterosexual woman who is Black. In the social context, the term "intersectionality"[51] is used to describe a framework for conceptualizing a person, group of people, or social problem as affected by discrimination and disadvantage. In the context used here, the term is meant to represent the "intersection" of dimensions of diversity in the analysis of response.

[49] The term Black is used throughout this Document per OMB, to represent "A person having origins in any of the black racial groups of Africa." *Note*: The term Black is used in this guidance instead of "Black or African American." In this document, whenever a publication has used the term "Black or African American" as a self-defined race category (e.g., in reporting study results), we have retained the designation. See Federal Register. Office of Management and Budget. Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity. Vol 81, No 190. 67398-67401. September 30, 2016. Available at: https://www.govinfo.gov/content/pkg/FR-2016-09-30/pdf/2016-23672.pdf [Accessed 24 May 2020].

[50] Per OMB, "A person having origins in any of the original peoples of Europe, the Middle East, or North Africa." *Note*: Outside the U.S., national ancestry has largely replaced the concept of race, and white is often used as an adjective to describe subgroups of a national heritage (e.g., white South Africans). See *ibid*.

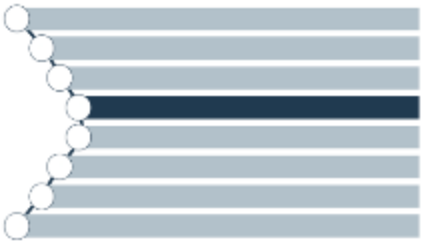
[51] Steinmetz K. She Coined the Term "Intersectionality" Over 30 Years Ago. Here's What It Means to Her Today. Time Magazine. February 20, 2020. (see: https://time.com/5786710/kimberle-crenshaw-intersectionality/) [Accessed 27 May 2020]

Because of the unique history of the U.S. as a nation formed largely from intentional immigration– sometimes forced, more often voluntary – of persons of various nationalities, races, ethnicities and religions, among other variables, issues of race and ethnicity are more salient in the United States than in many other countries. There is no "correct" definition or terms of use nor universally accepted classification of race and ethnicity; terms are highly personal, and "categories" of race and ethnicity are often not discrete. Therefore, in this document we have used the terms as currently directed by the U.S. Office of Management and Budget (OMB);[52] we appreciate that this decision is "U.S.-centric," but we felt that we needed one set of terms to use. OMB notes, and we agree, that "the racial and ethnic categories set forth in the standard should not be interpreted as being scientific or anthropological in nature."[53] Importantly, OMB specifies that a *minimum* of five categories will be used for reporting data on race, and two categories for reporting data on ethnicity, thereby acknowledging that additional categories exist.[54] OMB is currently reviewing the policy directive,[55] a review that we welcome. What is important is how individuals self-identify and that respect for those identities and individual dignity be preserved.

While similar issues exist in regions outside of the U.S., here we often draw upon case examples from the United States, and we focus on barriers and corrective actions that are generalizable, although the specific implementation may differ. In the U.S. and elsewhere, other aspects of diversity and related social determinants of health give rise to important examples of health

[52] Federal Register. Office of Management and Budget. Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity. Vol 62, No 210. 58782-58790. October 30, 1997. Available at: https://www.govinfo.gov/content/pkg/FR-1997-10-30/pdf/97-28653.pdf [Accessed 24 May 2020]
[53] Federal Register. Office of Management and Budget. Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity. Vol 81, No 190. 67398-67401. September 30, 2016. Available at: https://www.govinfo.gov/content/pkg/FR-2016-09-30/pdf/2016-23672.pdf [Accessed 24 May 2020]
[54] Notably, OMB states "The categories should set forth a minimum standard; additional categories should be permitted provided they can be aggregated to the standard categories," thereby suggesting that the additional categories should "roll up" to one of the five designated categories. Federal Register. Office of Management and Budget. Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity. Vol 81, No 190. 67398-67401. September 30, 2016. Available at: https://www.govinfo.gov/content/pkg/FR-2016-09-30/pdf/2016-23672.pdf [Accessed 27 May 2020]
[55] Federal Register. Office of Management and Budget. Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity. Vol 81, No 190. 67398-67401. September 30, 2016. Available at: https://www.govinfo.gov/content/pkg/FR-2016-09-30/pdf/2016-23672.pdf [Accessed 24 May 2020]

disparity. We anticipate and hope that the approaches suggested within this document are generally applicable to other settings and countries.



2.4 Research and the utility of subgroups

When considering the application of requirements of diversity across the product development program and to a specific research protocol, the research question itself is the primary consideration (see Section 13.1 "Product development and lifecycle" and Section 13.2 "Study question and design"). Studies conducted during product development, at a time when less is known about safety and efficacy of the product, will differ from later-phase research. The specific research question, condition under study, and research locale informs consideration of inclusion of specific subgroups and its importance. The following examples illustrate subgroup selection based on the research question at hand.

Figure 5: Case example: Edarbi & Edarbyclor

Case example: Azilsartan medoxomil (Edarbi®) & Azilsartan medoxomil/chlorthalidone (Edarbyclor®)

Azilsartan medoxomil (Edarbi®) is an angiotensin-II receptor blocker (ARB) used to treat hypertension in adults.[56] Designs of Azilsartan medoxomil phase 3 monotherapy trials were intentionally inclusive of Black patients, a population that more commonly exhibits low renin (the enzyme critical to helping control sodium balance) and reduced response to ARBs. The phase 3 trials of Azilsartan medoxomil did show a reduced effect in Black patients, a finding that is reflected in the prescription label, but was still safe and effective in reducing blood pressure regardless of age, sex, or race. Azilsartan medoxomil was approved by the FDA.

When investigating combination therapy for azilsartan medoxomil, developers specifically selected a diuretic that would accentuate the effect of the ARB in patients with low renin. Azilsartan medoxomil in combination with chlorthalidone (Edarbyclor®), was the most effective combination. In fact, wording in the drug product labeling states, "Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients; however, the blood pressure effect of Edarbyclor in blacks is similar to that in non-blacks."[57]

Hypertension in Black patients is often known to be of earlier onset, greater severity, and more frequently complicated by stroke, end-stage disease, congestive heart failure, and dementia.[58]

[56] Highlights of prescribing information. Edarbi. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/200796s000lbl.pdf [Accessed 27 May 2020]
[57] Highlights of prescribing information. Edarbyclor. Available at: https://www.edarbi.com/media/pdf/EDARBYCLOR-PI.pdf [Accessed 27 May 2020]
[58] See for instance, Lackland DT. Racial differences in hypertension: implications for high blood pressure management. The American journal of the medical sciences. 2014 Aug 1;348(2):135-8; Musemwa N, Gadegbeku CA. Hypertension in African Americans. Current cardiology reports. 2017 Dec 1;19(12):129; Murray MD, Hendrie HC, Lane KA, Zheng M, Ambuehl R, Li S, Unverzagt FW, Callahan CM, Gao S. Antihypertensive medication and dementia risk in older adult African Americans with hypertension: a prospective cohort study. Journal of general internal medicine. 2018 Apr 1;33(4):455-62; Hicken MT, Lee H, Morenoff J, House JS, Williams DR. Racial/Ethnic Disparities in Hypertension Prevalence. Community Health Equity: A Chicago Reader. 2019 Mar 29:173; Clark D, Colantonio LD, Min YI, Hall ME, Zhao H, Mentz RJ, Shimbo D, Ogedegbe G, Howard G, Levitan EB, Jones DW. Population-Attributable Risk for Cardiovascular Disease Associated With Hypertension in Black Adults. JAMA cardiology. 2019 Dec 1;4(12):1194-202.

It is also known that Black patients often respond differently to certain medications (e.g., angiotension converting enzyme inhibitors) than patients of Anglo-American descent.[59,60] Thus it is important to evaluate whether Black participants respond—in both safety and efficacy—similarly to White individuals, and even more critical to include a sufficiently large population of Black patients in a phase 3 study if phase 1 and 2 data demonstrated disproportionate safety events or efficacy[61] (see both Figure 5 and "Case Study: Omapatrilat" in *Toolkit*). History has shown these considerations are important: Omapatrilat, a novel investigational drug that inhibits both neutral endopeptidase (NEP) and angiotensin converting enzyme (ACE) designed to lower blood pressure, demonstrated promising initial results. However, a serious secondary adverse event (angioedema, or a rapid swelling [edema] below the skin or mucosa) occurred three times more often in Black than White patients (for more detail see "Case Study: Omapatrilat" in *Toolkit*). Further development of the product was abandoned. Had Black patients not been included in the clinical trials for product development, significant safety concerns would only have been identified post-approval, after the drug was introduced into the market, potentially impacting the lives of many more patients.

However, very different expectations arise when considering a randomized trial of 10-day versus a 14-day course of an antibiotic to treat a tick-borne infection. In this instance, it may be important to know which pathogen caused the tick-borne illness, and whether the enrolled population represented rural versus urban settings, temperate versus tropical climate, and/or the month of disease, as these are known to influence the manifestation of disease and treatment outcome. Whether the individual is male or female, adolescent or elderly (assuming

[59] See for instance: Weir MR, Gray JM, Paster R, Saunders E. Differing mechanisms of action of angiotensin-converting enzyme inhibition in Black and White hypertensive patients. Hypertension. 1995 Jul;26(1):124-30; Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clinical Pharmacology & Therapeutics. 1996 Jul;60(1):8-13; Palla M, Ando T, Androulakis E, Telila T, Briasoulis A. Renin-Angiotensin System Inhibitors vs Other Antihypertensives in Hypertensive Blacks: A Meta-Analysis. The Journal of Clinical Hypertension. 2017 Apr;19(4):344-50; Brown T, Gonzalez J, Monteleone C. Angiotensin-converting enzyme inhibitor–induced angioedema: A review of the literature. The Journal of Clinical Hypertension. 2017 Dec;19(12):1377-82; Kostis WJ, Shetty M, Chowdhury YS, Kostis JB. ACE inhibitor-induced angioedema: a review. Current hypertension reports. 2018 Jul 1;20(7):55.

[60] Anglo-American descent for this purpose reflects individuals whose native language is English and especially whose culture or ethnic background is of European origin.

[61] It may be less important to determine with the benefit and safety of an intervention is similar or identical across subpopulations and more important to provide affirmative evidence of effect within each subgroup (regardless of whether that effect is similar across subgroups). See Part D "Data Standards and Analysis."

pharmacokinetic and pharmacodynamic profiles are similar), however, may not be as impactful to the outcome. The study question, design, eligibility criteria, and analytic approach should be based on prior scientific and medical knowledge to the degree that information from one subgroup can be applied to another (see Chapter 12 "Approach to Data Analysis").

Similarly, in prospective treatments for psoriasis,[62,63] differences in absorption and response may depend on differences in skin pigmentation, exposure to sunlight, genetics, or other factors and may be less dependent upon sex or social determinants of health. Another example is that the efficacy of treatment for cystic fibrosis[64,65] or lung cancer[66,67] will be directly related to causative genetic mutations, and far less on other dimensions of diversity. Generally, the long-term safety of a treatment that will be taken for years may differ if the treatment is started in adolescence than in geriatric populations, given the differences in physiology, length of exposure, and presence or absence of comorbidities.[68]

Taken together, then, the research question, clinical paradigm, and prior knowledge of the disease or condition, in addition to the proposed intervention itself, will affect whether and when to consider different subgroups in research, and in trial planning and analyses, usually in consultation with regulators. 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 of differences are helpful. Case-based analyses are necessary.

---

[62] Kaufman BP, Alexis AF. Psoriasis in skin of color: insights into the epidemiology, clinical presentation, genetics, quality-of-life impact, and treatment of psoriasis in non-white racial/ethnic groups. American journal of clinical dermatology. 2018 Jun 1;19(3):405-23.
[63] Alexis AF, Blackcloud P. Psoriasis in skin of color: epidemiology, genetics, clinical presentation, and treatment nuances. The Journal of clinical and aesthetic dermatology. 2014 Nov;7(11):16.
[64] Corvol H, Thompson KE, Tabary O, Le Rouzic P, Guillot L. Translating the genetics of cystic fibrosis to personalized medicine. Translational Research. 2016 Feb 1;168:40-9.
[65] Fajac I, De Boeck K. New horizons for cystic fibrosis treatment. Pharmacology & therapeutics. 2017 Feb 1;170:205-11.
[66] Wang DC, Wang W, Zhu B, Wang X. Lung cancer heterogeneity and new strategies for drug therapy. Annual review of pharmacology and toxicology. 2018 Jan 6;58:531-46.
[67] Turajlic S, Sottoriva A, Graham T, Swanton C. Resolving genetic heterogeneity in cancer. Nature Reviews Genetics. 2019 Jul;20(7):404-16.
[68] Comorbidities and polypharmacy are generally important considerations with advancing age.

2.5 Clinical research settings and subgroup analyses

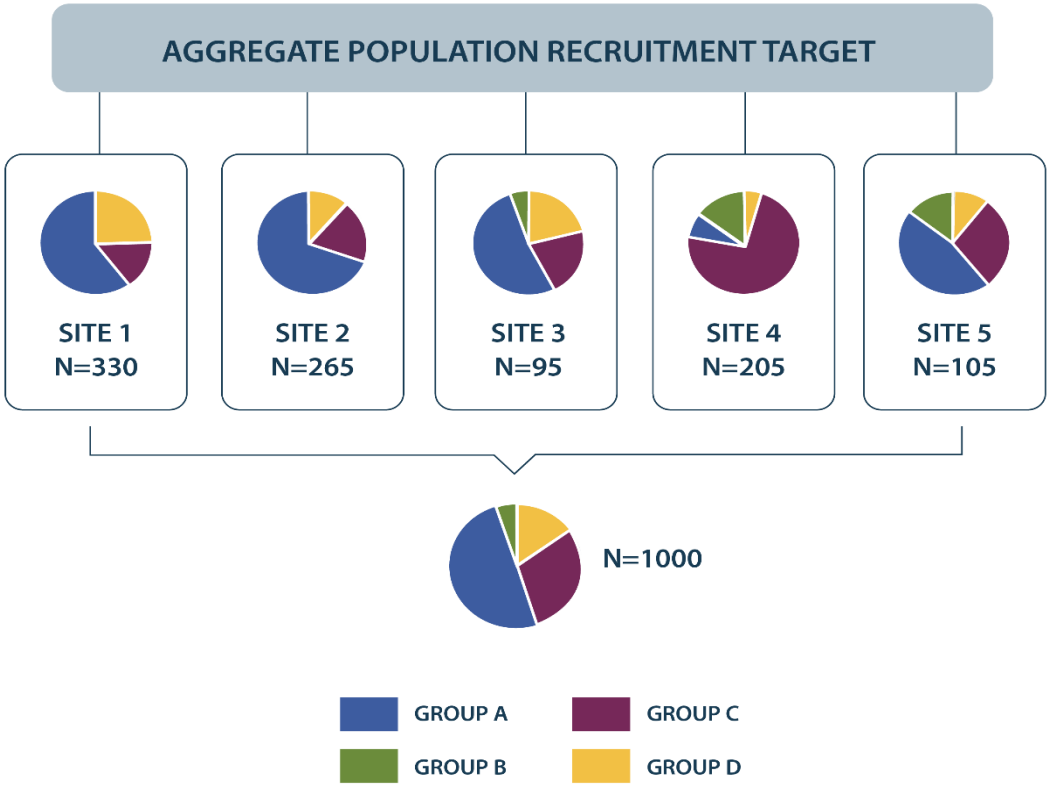
While some clinical trials are conducted at a single institution, the majority of trials are multi-site and often multi-national. Therefore, it is the aggregate population, not the site-specific accrual to trials, that matters for the analyses of data (see Figure 6). In other words, not every individual site needs to recruit representative populations, but the aggregate number of enrollees—in its entirety—should reflect the intended distribution.

Diverse representation may be achieved through recruitment of different sites that serve different populations, whether that be in multi-site or multi-national research. However, this requires advanced planning: sites need to predict and deliver on the relative diversity (in whatever dimension of diversity that is important to the research) of the population, informed by the catchment area (see Section 13.4 "Feasibility assesments and site selection" and "Feasibility Decision Tree" and "Feasibility Questionnaire Modification Checklist" in *Toolkit*). The promise of diverse representation in pivotal and other clinical trials, however, has not been achieved by multi-national recruitment. Over 80% of marketing applications to the U.S. Food and Drug Administration (FDA) for drugs and biologics contain data from ex-U.S. studies.[69] A study conducted from 1999-2012 in 163 countries that examined 205,455 clinical trials from 15 global primary trial registries observed a shift in clinical research from high-income countries to low- and middle-income countries, particularly to Asia, Latin America and other emerging economies.[70] Nevertheless, at least for pivotal studies in which the data are available, greater international outreach did not result in inclusion of underrepresented ethnic and racial subgroups as to reflect either the demographics of the disease or of those likely to use the intervention.[71,72]

---

[69] Levinson DR, General I. Challenges to FDA's ability to monitor and inspect foreign clinical trials. Washington, DC: Department of Health and Human Services Office of Inspector General. 2010 Jun.
[70] Drain PK, Robine M, Holmes KK, Bassett IV. Trial watch: global migration of clinical trials. 2014 Feb 28; 13(3):166-167.
[71] U.S. Food and Drug Adminstration. Drug Trials Snapshots. Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots. [Accessed 27 May 2020]
[72] As noted previously, one might hypothesize that since clinical trials are not generally powered to detect a difference between subgroups, inclusion of a diverse population is not necessary nor informative. We reject that

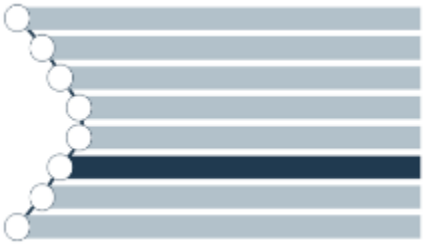
Figure 6: Aggregate population



In this example, the planned clinical trial is intended to enroll an overall population that mimics the prevelance of disease by race and ethnicity (Groups A-D); all the data collected are included for the analysis of the primary outcome. In a *single-site* trial, therefore, the percentage diverse representation must be achieved by enrollment at that individual site. In a *multi-site* trial, however, it is the aggregate of all the sites that is important; any one site may underrepresent or overrepresent a given subgroup. Planning, site feasibility assessment, and dynamic tracking of enrollment is therefore particularly important (see Section 13.4 "Feasibility assessments and site selection").

hypothesis. While it is true that diverse inclusion is often not necessary to achieve the scientific goals, it is necessary to achieve social goals. Similarly, inclusion that meets social justice imperatives may not be sufficient to achieve the scientific goals. These are different but interwoven objectives: understanding variability (scientific goals) and social justice (ethical goals), as well as maximizing opportunities to detect unique insights from a more diverse study population.

The issues of subgroup analysis raised here parallel those that sovereign health regulatory authorities (HRAs) address routinely in determining whether an intervention is equally or equivalently safe and effective for the citizens in their countries. National health authorities are responsible for reviewing and approving products for their population, a population that is defined by geographic boundaries and not necessarily by intrinsic biological differences. In this setting, regional or country-specific differences represent just a different "subgroup" to be analyzed. Indeed, ICH E5(R1)[73] and ICH E17[74] directly address the scientific and statistical complexities of subgroup analyses. Adequate characterization of pharmacokinetics, pharmacodynamics, dose-response, efficacy, and safety in the specific population (in this example, country or regional populations) is necessary. The same considerations apply to the analysis of any subgroup.



2.6 Analyzing a population but treating an individual

The objectives of clinical research in humans is generalizable knowledge; the results of a clinical trial reflect the average treatment effect for the population enrolled in the trial. While knowledge that results from trials is based on aggregate data, what matters for any individual, and for the healthcare provider caring for that individual, is whether the product or intervention will be safe and effective for that individual.[75] Generalizable knowledge is useful only in so far as it reflects the population most like (i.e., most similar to) that individual. The shift in healthcare towards personalized medicine

[73] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline. Ethnic factors in the acceptability of foreign clinical data E5(R1). 5 February 1998. Available at: https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf [Accessed 10 January 2020.]

[74] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonized guideline: General principles for planning and design of multi-regional clinical trials. ICH E17. 2017. Available at: https://database.ich.org/sites/default/files/E17EWG_Step4_2017_1116.pdf [Accessed 27 May 2020]

[75] Ahmed M, D Kent, J Paulus, and D Whicher, editors. Caring for the Individual Patient: Understanding Heterogeneous Treatment Effects. Washington, DC: National Academy of Medicine.; 2019. Available from: https://nam.edu/wp-content/uploads/2019/08/Caring-for-the-Individual-Patient-prepub.pdf. [Accessed 27 May 2020]

reflects the appreciation that every individual is unique and that the response to any intervention may differ between and among individuals. However, healthcare providers and the patients themselves make individual decisions on an evidence base that is derived from analyses at the population level. As the 2019 National Academy of Medicine workshop publication, focused on understanding heterogeneous treatment effects, stated:

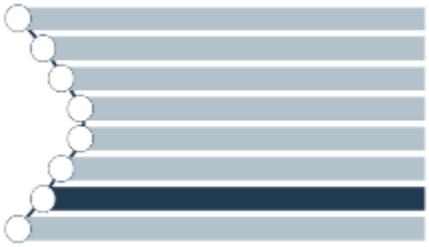
> … for evidence to be more applicable at the individual patient level, we need to combine methods for strong causal inference (e.g., randomization) with methods for prediction that permit inferences about *which* particular patients are likely to benefit and which are not.[76]

Clinical trials do not account for personal preferences and choice. Two individuals with the same serious disease may choose very different paths for treatment. The best research data can inform decision-making, and therefore data on heterogeneity of treatment effects are important to the individual, but population data may not be determinative nor reflective of an individual's values and choices.

The challenge of interpreting results derived from a population to apply to an individual patient is at the core of an irresolvable tension. The results of a clinical trial enrolling a homogeneous population will apply well to the individuals in that trial and others exactly like them, but may not apply well to a patient from the more heterogeneous patient population outside the demographics of and external to the trial. On the other hand, the greater the diversity of the population enrolled in a clinical trial, the more variability and heterogeneity there will be in outcome, and the average result may be less likely to reflect the characteristics of any individual patient. A more diverse clinical trial population simply allows a better understanding of the degree to which we should be concerned about generalizability, or heterogeneity of effect (see Section 13.3 "Eligibility criteria"). More sophisticated analyses of subgroup differences may better approximate the likelihood of individual differences. In the end, what matters to the individual patient is whether the treatment or intervention will be beneficial, whether that potential benefit outweighs the potential risk of harm, and the degree of certainty that these predictions will hold. In other words, "will that treatment work for *me*?" New

[76] Ahmed M, D Kent, J Paulus, and D Whicher, editors. Caring for the Individual Patient: Understanding Heterogeneous Treatment Effects. Washington, DC: National Academy of Medicine.; 2019. Available from: https://nam.edu/wp-content/uploads/2019/08/Caring-for-the-Individual-Patient-prepub.pdf. [Accessed 27 May 2020]

methodological, statistical, and data-driven approaches, such as machine learning analyses of post-marketing, real world data derived from well-defined populations, are needed.

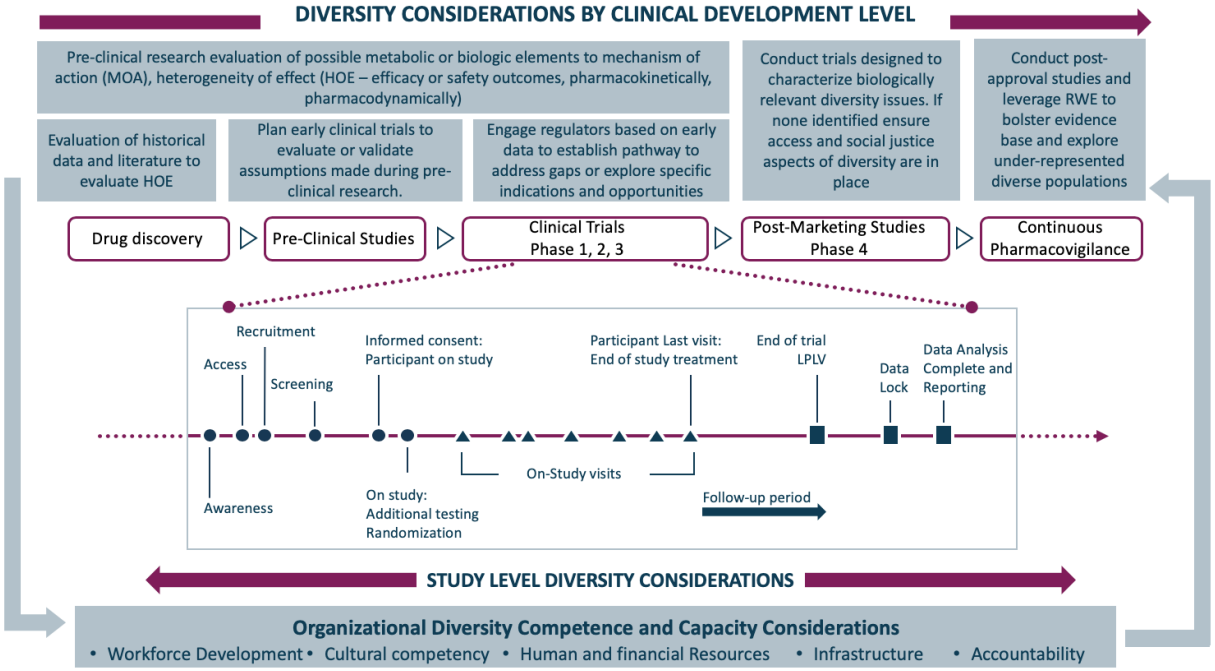


2.7 Product development, clinical trials, and real world heterogeneity

The traditional product development paradigm involves an orderly progression from discovery to pre-clinical testing (including toxicology, animal testing, pharmacokinetics, and pharmacology[77]) to phase 1, 2, 3 studies, to review and approval by the cognizant regulatory authority (Figure 7). Thereafter, an approved product is introduced into the market for general use and may undergo further study to gather additional information on safety, efficacy, and/or optimal use.

[77] Pharmacokinetics and pharmacology include absorption, distribution, metabolism, and excretion.

Figure 7: Product development pathway



Traditional product development includes interacting considerations of diversity that span throughout drug development - from early drug discovery, pre-clinical research, clinical trials development, and to post-marketing approval and pharmacovigilance. From the start of drug discovery and pre-clinical studies, widespread evaluation for mechanisms of action (MOA) and potential heterogeneity of effect (HOE) need to be prioritized to inform further research and development. At the clinical study level, and throughout all trial phases, organizations need to consider and proactively plan for recruitment and retention of a diverse study population that are reflective of potential heterogeneity of prevalence, or effect/outcomes. Organizations should consider putting in place checkpoints and mechanisms to assess assets diversity planning as they progress through stage-gates (from pre-clinical to early clinical and at phase 1/2 transition for example) that diversity is a consideration for effective planning. Simultaneously, organizations need to consider the competence of their workforce and capacity of the organization to appreciate and emulate the importance of diversity and inclusion within the organization and its product portfolio.

There are differences between the well-controlled settings of phase 1-3 clinical trials, post-marketing trials, observational trials and real world evidence (i.e., experience). Clinical trials often have well-controlled eligibility (i.e., inclusion/exclusion) criteria, in part to minimize the risks inherent in research on products for which little information is known (see Section 13.3 "Eligibility criteria"). Therefore, they may not reflect the diversity of the real world population that is or will be treated.[78] Further, many studies are shorter in duration than the duration of exposure after approval. But there are additional differences that are inherent in the post-market setting, including the difficulty in assessing medication adherence to the intended schedule (e.g., timing, dose) as well as to the approved indication. Thus, it is important to consider the entire drug development program, from early phase trials to novel, complex clinical trials to post-marketing observational data. Real world evidence can also be deployed to inform product development, even at the point of the initial stages of development and translation. As discussed further below, if real world evidence is to be utilized, however, it is important to ensure that the data sources have adequate and sufficient representation of different demographic subgroups.

Many safety events cannot be identified or predicted from clinical trials; low-frequency events, for instance, often require observational data collected or reports from events observed from millions of treated individuals, not the smaller number (even thousands) involved in clinical trials. Pharmacovigilance systems have been developed to capture these events, and it is not uncommon for new safety information to emerge, particularly in the first few years after market approval.

Just as the complete safety profile cannot be adequately assessed from early clinical trials, subgroup differences in treatment (therapeutic) effect cannot be determined adequately from the clinical product development pathway. Analyses will depend upon data collected from the varied and disparate populations treated after introduction into general use, and new systems to capture that data going forward will be necessary. Thus, global standardization of data elements, metadata, data dictionaries, and common data collection methods are essential to make appropriate use of observational and trial data, and to make appropriate and timely

[78] In the absence of the randomization of clinical trials, patient characteristics (e.g., severity of illness) are likely to influence the clinician's decision about whom to treat with a particular product.

progress. Armed with data that follows the FAIR (Findable, Accessible, Interoperable, and Reusable) Guiding Principles,[79,80] the opportunity, power, and importance of real world data and real world evidence as they relate to diversity will only grow.

The need to collect data from the "real world" in order to augment the benefit and risk profile of an intervention extends to personalized medicine, wherein the population treated in a trial is by definition limited. The same applies to treatments of rare and ultra-rare diseases and to patients with unmet medical needs, where withholding apparently beneficial interventions, as may occur in a clinical trial, may not be appropriate. The same logic applies to novel and innovative treatment paradigms such as gene therapy, regenerative and cellular therapies, tissue engineering, and 3-D printing.

To address emerging sciences, trial designs have evolved, from traditional randomized clinical trials (RCTs) to complex study design including adaptive trials in all their variations, platform or master protocols, and others (e.g., N of 1 trials) (see Section 13.2 "Study question and design"). In addition, regulatory expectations have also evolved, and many countries have implemented regulatory pathways to accelerate patient access to treatment. The European Medicines Agency (EMA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) have introduced pathways of "conditional approval;"[81,82] EMA has initiated accelerated assessment and approval pathways,[83] and the U.S. FDA has priority review, breakthrough therapy, accelerated approval, and fast track pathways.[84] These pathways allow access to therapies but

[79] Wilkinson, M., Dumontier, M., Aalbersberg, I. *et al.* The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* ***3,*** 160018 (2016).
[80] Wilkinson, M.D., Dumontier, M., Jan Aalbersberg, I. *et al.* Addendum: The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* **6,** 6 (2019).
[81] Sipp D. Conditional approval: Japan lowers the bar for regenerative medicine products. Cell Stem Cell. 2015 Apr 2;16(4):353-6.
[82] European Medicines Agency. Support for early access—Accelerated assessment. Available at https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment [Accessed 17 July 2020].
[83] European Medicines Agency. Support for early access—Accelerated assessment. Available at https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment [Accessed 17 July 2020].
[84] U.S. Food and Drug Administration. Fast track, breakthrough therapy, accelerated approval, priority review. Available at https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review [Accessed 27 May 2020].

with the expectation of further collection of quality data and periodic reassessment of benefit and risk, using real world data, with regulatory review, including potential anticipated changes to the label and/or approval itself. Real world data and observational studies should be considered in the continuum of understanding of the product, and therefore built into the product lifecycle.

Research outside the traditional clinical trial paradigm will afford new opportunities to plan and execute studies examining variability across subgroups. It is important to emphasize that the burden—and opportunity—of inclusion applies to all sponsors of clinical trials, and does not rest solely with manufacturers. Equally important is research funded by academia, for-profit healthcare companies other than innovator companies, government agencies engaged in health, and non-profit sponsors. The opportunity to address safety, efficacy, and effectiveness as it applies to all populations extends not only beyond the product development pathway and marketing approval but to all clinical research. Academic researchers and others have the capability to address heterogeneity of treatment effect using real world and observational data. In some cases, such as behavioral interventions or biorespository studies, the importance of diversity and inclusion may be even more of a priority, in that an obligation to address social justice and health equity concerns may be a direct objective of the research.

2.8 The business value of inclusion of diverse populations

The "business" case, or value proposition, for increasing diversity in clinical research involves both potential benefits and cost considerations—not only the costs of achieving diversity but the cost impact of not having or achieving diversity.

There are several perceived challenges to inclusion. The first relates to a concern that increasing diversity and heterogeneity of the participant populations will introduce some "uncertainty" in the relevant outcome, particularly when trial results will be compared to prior

trials. Second, it may introduce higher risk or treatment resistant populations, and while it is important to identify these differences at some point, this concern represents "risk" during product development. Third, product development trials are often and intentionally multi-national. In that setting, representation of the enrolled populations must be balanced so that regulators around the world can review data from their regional populations. Fourth, increasing diverse populations may lead to increasing variability of treatment effect, and therefore the sample size requirement will increase. Widening the age range, for instance, might have this impact.[85] Finally, there is the concern for increased costs, both in length of time to trial completion as well as resources required to recruit and retain appropriate participation. There is little published empirical data to support the claim that increasing diversity increases cost, and this should be an area of future analysis.[86] In the spirit of equity, rather than simply equality, increased initial investment is expected and may be needed to achieve these diversity goals across all groups. The perceived increase in costs appear to relate to addressing diversity *late* in trial planning and execution, or seeking statistical significant population sizes across a large array of demographic subgroups. On the latter point, planning for subgroup analyses with statistical significance would delay product development and be financially untenable, but planning a logical and risk-based expansion of some subgroups is possible. Indeed, the development of a road map to expanding the population or specific trials in the relevant populations locally or regionally—and not affecting global representation—should be part of the product development plan.

With regard to a single clinical trial, the question is whether *planning* for diversity—rather than *correcting* for a lack of diversity during study implementation (e.g., including appropriate sites rather than adding additional sites, inclusive eligibility criteria rather than processing

[85] In this regard, it is important to distinguish between *prognostic* factors and *predictive* factors. A prognostic factor is one that's related to the clinical outcome, although not necessarily to the drug's effect. For example, older patients might have poorer outcomes than younger patients, even if they benefit from the treatment just as much as younger patients. A predictive factor is one that's specifically related to the drug's effect. For example, Black patients may not benefit from some anti-hypertensive medications as much as White patients. Our interest is in predictive factors (i.e., heterogeneous treatment effects), which are probably somewhat uncommon, but it is the prognostic factors that influence variability and sample size. Notably, however, the impact of prognostic factors on sample size can be mitigated by stratified randomization and covariate analysis.

[86] Additionally, there is no reason *a priori* to anticipate that a diverse population will have an inferior response to an intervention or have more adverse events. The diverse population may respond better, more quickly, and with less toxicity. Only empirical data will answer the question.

amendments to modify eligibility criteria, Institutional Review Board/Independent Ethics Committee [IRB/IEC] amendments, new IRB/IEC approvals, all of which incur time delays and impact logistics)—would change the cost calculations. As one example of costs, analysis of substantial global amendments of industry-sponsored trials has shown that the cost per amendment averages ~$150,000 for a phase 2 trial and ~$535,000 for a phase 3 trial, and each trial averaged over 2 substantial amendments.[87] Certainly, late course-correction in an ongoing trial to recruit additional or different populations may delay trial completion and incur additional financial costs. But whether the costs are increased in a trial that has been appropriately and proactively planned to enroll a diverse population is not clear. In this caser, the axiom "an ounce of prevention is worth a pound of cure" may likely be true. In fact, broader eligibility requirements and more flexible study procedures may promote faster enrollment at decreased or equivalent cost.

Throughout Section 13.5 "Study conduct, recruitment and retention," we focus on identifying and overcoming the barriers that currently impede inclusion and on approaches to more efficiently identify, engage, recruit, and retain populations of interest. In Chapter 12 "Approach to Data Analysis" we discuss how to analyze new data sources for relevant information, and novel analytic approaches. Progress will depend upon uniform definitions for categories of interest, so that data, in time, become interoperable (see Chapter 11 "Data Variables and Collection"). In Chapter 16 "Genetics and Clinical Research Diversity," we focus on how genomic and pharmacogenomics research, meta-analyses, registries, biobanks, and data repositories can each be leveraged to supplement clinical research data and shape clinical development as it applies to currently underrepresented groups.

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. We will briefly review the positive and potential negative drivers of making that initial investment.

[87] Getz KA, Stergiopoulos S, Short M, Surgeon L, Krauss R, Pretorius S, Desmond J, Dunn D. The impact of protocol amendments on clinical trial performance and cost. Therapeutic innovation & regulatory science. 2016 Jul;50(4):436-41.

2.8.1 Potential positive incentives

There are a number of positive drivers to inclusion of diverse population. Some of the most important are listed in Table 1.

Table 1: Potential positive incentives

POTENTIAL POSITIVE INCENTIVES
Improved scientific credibility
Meeting social responsibility
Improved financial performance
Increased public confidence and trust
Enhanced reputation, social capital
Increased compliance with regulatory expectations
Better compliance with funder expectations

We have previously discussed the **scientific goal** of understanding heterogeneity of treatment effect as a consequence of the knowledge gained from clinical trials. Beyond understanding scientific variability throughout product development, it is important to recognize that if the populations represented in our research databases are reflective of the intended users, resources can be better focused in areas that need further study following approval. Appropriate representation in research databases also provides a controlled backdrop for evaluation of benefits and risks that may emerge with real world usage (e.g., spontaneous adverse event reports, analysis of real world data, outcomes of observational or database studies). While neither may be persuasive on its own (for example, a sub-group analysis from an RCT and an outcome from an observational study), if one appears to provide a signal and the other trends in the same direction, swifter action (or the prevention of an over-reaction to a potentially spurious signal) may be possible. More representative and controlled data to support the scientific evidence base will strengthen the analyses by manufacturers (and learning health care systems), and potentially result in more specific and resilient **product labeling**, create fewer "surprises" after approval, and increase **public confidence**.

We previously discussed the societal benefit regarding the need to develop necessary and appropriate treatments for all patients and of offering equal access to clinical trial participation. Every organization has responsibilities to the public: for-profit companies are accountable financially to their shareholders, but they also commit to corporate **social responsibility** as a component of sustainability and long-term value.[88] A meta-analysis has shown that corporate social responsibility correlates positively with corporate **financial performance**,[89] and that correlation is greater in mature institutions and developed economies.[90] More importantly, pharmaceutical and device companies are in the business of developing products to improve the health and well-being of individuals, to improve and save lives. Similarly, the mission of academic and non-profit sponsors is in part to advance public health. A commitment to diversity is a part of these responsibilities,[91] and will perforce, contribute to **reputation**, **social capital, public confidence, and trust.**

While a number of regulatory authorities have not mandated or defined enrollment for specific subgroups, in the U.S., legislative actions have strengthened the oversight of representativeness by regulatory authorities. The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012[92] directed the U.S. FDA to investigate and report on the inclusion and quality of demographic subgroup analyses (i.e., sex, age, race and ethnicity) in applications for drugs, biologics and devices. Section 907 of FDASIA directed the "Food and Drug Administration [to issue] a report … addressing the extent to which clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups including sex, age, race, and ethnicity, is included in applications submitted to the Food and

[88] Demirag I, editor. Corporate social responsibility, accountability and governance: Global perspectives. Routledge; 2018 Oct 8.
[89] Additionally, if a company enrolls a specific population and can demonstrate that their product is safe and efficacious in that population—or even more safe and efficacious than other marketed treatments for the condition—then these findings will become a differentiator and may even result in better labeling.
[90] Wang Q, Dou J, Jia S. A meta-analytic review of corporate social responsibility and corporate financial performance: The moderating effect of contextual factors. Business & Society. 2016 Nov;55(8):1083-121.
[91] Ahmed HR, Strauss DH, Bierer BE. Committing to the Inclusion of Diverse Populations in Clinical Research. Therapeutic Innovation & Regulatory Science. 2020 Jan 2:1-3.
[92] Public Law 112-144, 112th Congress, entitled the Food and Drug Administration Safety and Innovation Act, signed into law July 9, 2012. https://www.govinfo.gov/content/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf [Accessed 27 May 2020]

Drug Administration, and … provide such publication to Congress."[93] The FDA followed with their *Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data*[94] that included three initiatives aimed at improving the (1) quality of reporting of demographic subgroup data; (2) participation, or the identification of barriers and strategies to improve subgroup participation; and (3) transparency, or improved public visibility of demographic subgroup data (see Section 17.9 "Regulatory agencies" of this Guidance Document). The FDA reviews demographic data on all FDA-regulated trials and is committed to publishing those data on each new molecular entity (NME) and original biologic approved by the agency within 30 days of its approval, focusing on subgroup data and analysis when available. Annually, the FDA publishes the data summary (see Section 5.2 "FDA Drug Trial Snapshots"), positioning the agency to compare data by therapeutic area and location of trial. The increase in transparency is helpful for identifying trends in pivotal trials over time. Outside the U.S., regulatory agencies from a number of countries (e.g., China, Japan) require, or look for, representation of their population in pivotal clinical trials in order to determine whether or not the investigational product appears to be equivalently safe and efficacious. For example, in China and Japan, there is published guidance on the need to include Chinese and Japanese patients in global RCTs in order to submit a product for consideration for regulatory approval. Inclusion of representative populations will help sponsors and investigators **align** with regulatory expectations in the U.S. and elsewhere.

Funders are also increasing their oversight of plans regarding trial participant recruitment, and some have published their expectations (see Section 17.2 "Industry sponsors and other entities that provide funding for clinical research"). The U.S. National Institutes of Health (NIH) has required the inclusion of women and minorities as participants since the U.S. Congress passed the NIH Revitalization Act of 1993,[95] the NIH Grants Policy has explicit directions for grantees to

[93] Public Law 112-144, 112th Congress, entitled the Food and Drug Administration Safety and Innovation Act, signed into law July 9, 2012. https://www.govinfo.gov/content/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf at p. 1093 [Accessed 27 May 2020]

[94] FDASIA Section 907: Inclusion of Demographic Subgroups in Clinical Trials. https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fdasia-section-907-inclusion-demographic-subgroups-clinical-trials. [Accessed 27 May 2020]

[95] National Institutes of Health. NIH guidelines on the inclusion of women and minorities as subjects in clinical research. Fed Regist. 1994; 59:14508–14513; and National Institutes of Health. NIH guidelines on the inclusion of women and minorities as subjects in clinical research. *Fed Regist*. 1994;59:14508-14513.

address the inclusion of women and minorities,[96] and the NIH has routinely published statistics on clinical trial participation.[97] Recently, the NIH clarified and strengthened its clinical trial inclusion requirements, focusing on applicable NIH-funding for phase 3 trials, to "ensure results of valid analyses by sex/gender, race, and/or ethnicity are submitted to Clinicaltrials.gov."[98] While no enforcement actions have yet been established, funding agencies are cognizant of the necessity to include appropriate populations in research.

Finally, **insurers and third party payors** may begin to look for evidence of efficacy in subgroups in making both payment and formulary decisions.[99] More importantly, affirmative data that show efficacy and safety for various populations will strengthen arguments for access, wide distribution and uptake, payment, and reimbursement.

2.8.2 Potential costs to lack of inclusion

It seems equally important to question the potential costs (e.g., corporate and public responsibility, lost revenue, opportunity costs, health disparities, trust) of *not* having diverse representation. A number of potential opportunity costs for failing to include diverse populations exist (see Table 2).

[96] NIH Grants and Funding. Inclusion of Women and Minorities as Participants in Research Involving Human Subjects. Available at: https://grants.nih.gov/policy/inclusion/women-and-minorities.htm [Accessed 27 May 2020]
[97] NIH NCDC Inclusion Statistics Report. Available at: https://report.nih.gov/RISR/#/ [Accessed 27 May 2020]
[98] Amendment: NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. NOT-OD-18-014. Available at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-014.html. [Accessed 27 May 2020]
[99] On the other hand, vigilance will be required to make sure that subgroup analyses are not misinterpreted or misused, leading to discrimination that further excludes or deprives underserved populations.

Table 2: Potential costs to lack of inclusion

COSTS OF NOT BEING INCLUSIVE
Decrement in market capital and share
Impact on labelling
Reputational loss
Narrow use and/or uptake of product
Liability for post-approval safety events
Expense of product withdrawal
Direct patient care costs of adverse events
Public scrutiny

Financial performance of clinical research depends on many factors: financial performance may benefit from diverse representation in clinical trials or suffer from the lack of it. Importantly, science should drive the degree of intentional overrepresentation or independent study of subgroups. When there is representation in clinical research of a subgroup that is expected to experience the disease, then the evidence base should summarize the dosing and benefit-risk for that subgroup in the label, if the evidence is scientifically sound. In its absence, little can be said specifically about that subgroup. Notably, currently there are few regulatory consequences to the lack of inclusion, but we suspect that will change. Today, the narrow eligibility criteria and recruitment targets do not generally result in a product label that is restricted to the enrolled population demographic, and cynically one could argue that any intentional lack of diversity may be intended, conscioiusly or subconsciously, to optimize the uniformity of results.[100]

[100] Thus, if there is insufficient diversity to detect a difference, and a manufacturer will nevertheless be given the broader label, there appears to be little incentive to diversify the population in a pivotal trial. Often, for instance, individuals of advancing age or those with organ dysfunction are not eligibile to enroll in investigational trials (primarily for potential safety concerns), but the eventual labels of tested products do not include such limitations in understudied populations. Thus, the product is tested primarily on a narrower population than for which it is approved, unless of course there is evidence of differential benefit or risk.

Several arguments, however, should be made that weaken the argument that preferentially enrolling a narrow population for pivotal trials is better. First, the excluded populations have an equivalent potential to have a more—rather than less—robust response to an investigational product than the narrower demographic, and one may miss the opportunity to detect a positive outcome (or negative) from product use. For example, the observation that a combination of isosorbide dinitrate and hydralazine (BiDil®) appeared more effective in patients with heart failure that were self-described African-Americans than in others led to a further trial specifically enrolling that population; the combination medication BiDil® was subsequenty approved by the FDA specifically for self-described African-Americans to be used in addition to routine heart failure medicines. Had an adequate number of African-Americans not been enrolled in the earlier studies, this observation may have been missed. While this situation was unusual, it points to the value of inclusion in clinical trials.

Second, as mentioned above, regulators and funders, and insurers and payors, may soon expect the clinical trial population to represent those for whom the product is intended. It is rapidly becoming the societal expectation that clinical trials will be representative in this way; its absence has been the focus of significant negative media attention.[101, 102, 103, 104] Patients, their families and caregivers, and physicians increasingly wish to see evidence that a product is safe and effective in comparable patients (e.g., "patients that look like me"); providing the evidence

[101] Editors T. Clinical Trials Have Far Too Little Racial and Ethnic Diversity [Internet]. Scientific American. Scientific American; 2018 [cited 2020Mar4]. Available from: https://www.scientificamerican.com/article/clinical-trials-have-far-too-little-racial-and-ethnic-diversity/

[102] Chen C., Wong R., Black patients are being left out of clinical trials for new cancer therapies [Internet]. STAT. 2018 Available from: https://www.statnews.com/2018/09/19/Black-patients-cancer-clinical-trials/ [Accessed 27 May 2020].

[103] Panner M. Diversity Is Severely Lacking Among Clinical Trial Participants -- How Can We Solve This Problem? [Internet]. Forbes. Forbes Magazine; 2019 Available from: https://www.forbes.com/sites/forbestechcouncil/2019/10/15/diversity-is-severely-lacking-among-clinical-trial-participants-how-can-we-solve-this-problem/#45c3e9c211a7 [Accessed 27 May 2020].

[104] Thielking M., Many clinical trials for new cancer drugs didn't include any data on race [Internet]. STAT. 2019 Available from: https://www.statnews.com/2019/08/19/clinical-trials-data-race/ [Accessed 27 May 2020].

base to support product use is not only the "right thing to do" but may **increase patient trust, provider confidence, product uptake and market share**.[105,106]

Third, following regulatory approval and introduction into the market, a product is made generally available for use by "real world" populations (e.g., individuals of varying age and race and ethnicities, with comorbidities, on multiple medications, and with organ dysfunction) and often for a far longer time period than on the pivotal trial. Safety events—or limited benefit in certain subpopulations—may emerge. These rarely require a change of label and, even more rarely, withdrawal of the product but each event has costs incurred (e.g., direct patient care costs, regulatory costs, financial expenses of the label change and communications, and loss of public confidence).[107] Analysis of 167 U.S. FDA-approved new medical entities (NMEs) from 2008-2013 demonstrated that approximately 21% reported some variability with respect to race and ethnicity in pharmacokinetics, safety, efficacy, dosing or pharmacogenetics.[108] Recommendations for dose adjustments listed in the product label were reflected in the minority of products in which there was an efficacy or safety impact; post-marketing studies were required for four. Thus, race or ethnicity may impact **labeling**, which is of larger financial consequence if discovered after approval. More significantly perhaps is the **potential liability** for individual or class action adverse events stemming from their discovery at a later stage; the manufacturers' intentions are easier to defend if there were an effort to discover subgroup-specific adverse events during product development.

Of course, it is common for problems with safety or efficacy to be discovered after product approval as the number of individuals exposed to the product increases substantially.[109] Even with diverse representation in clinical trials, the numbers of treated individuals will be small, and findings may not be conclusive. Thus, continued long term surveillance in diverse population groups can identify potential problems more quickly; active surveillance is an

[105] O'Connor MI. Equity360: Gender, Race, and Ethnicity—The Business Case for Diversity. Clinical Orthopaedics and Related Research®. 2019 May 1;477(5):948-51.
[106] Zusterzeel R, O'Callaghan KM, Caños DA, Sanders WE, Marinac-Dabic D, Strauss DG. Improving the safety and effectiveness of medical device therapy in women. Journal of Women's Health. 2016 May 1;25(5):428-30.
[107] Business analysts may argue that the revenue from early product approval and market uptake outweighs the costs of later label change, product withdrawal, or liability for adverse events.
[108] Ramamoorthy A, Pacanowski MA, Bull J, Zhang L. Racial/ethnic differences in drug disposition and response: review of recently approved drugs. Clinical Pharmacology & Therapeutics. 2015 Mar;97(3):263-73.
[109] These adverse events include some very rare events that are typically only identified after market introduction and increased use.

important responsibility of sponsors. Reputations rest in part on the central question of what was known and when, or what should have been known and when, by the manufacturers. The potential impact of product liability, damages, adverse publicity, and loss of public trust prevails if sponsors have only proven safety and efficacy in a subset of the demographics of the intended patient population and if post-approval surveillance is inadequate.

2.9 Conclusion

The goal of diversity in clinical research reflects a scientific, ethical, and clinical priority for public health. Its primary scientific purpose is to understand the influence of age, sex, race, ethnicity, and non-demographic factors as direct and indirect mediators of biological variability in treatment outcome. Diversity in clinical research may also provide evidence to examine the role played by social determinants of health in treatment response. Inclusion of populations across dimensions of diversity should be intentional and planned. The ethical and clinical mandates are synonymous: doing so ultimately advances health equity, fairness and justice, while providing for more reliable data, better patient outcomes, and improved possibilities to promote public health.

3. Basic Principles

The MRCT Center Diversity Workgroup has developed a set of fundamental principles that help to frame considerations of diverse representation in clinical research. While we recognize that a case-based analysis will be required for each clinical research question, we also believe that these principles will help guide those analyses:

3.1 Efforts to ensure diversity and inclusion in clinical research endeavor to be responsive to the ethical principle of justice by promoting greater fairness in the distribution of the benefits and risks of the research.[110]

The clinical research enterprise—and healthcare – should endeavor to distribute the risks, burdens, and benefits of research fairly and responsibly. The health needs, and responses to interventions, of populations and individuals can only be identified, considered, and managed if those populations and individuals are represented and studied.

3.2 Race, ethnicity, sex, gender, age, and geographic ancestry do not define distinct genetic or biological groups; yet along with social, cultural, and economic factors, these factors can be associated with important differences in disease susceptibility and manifestation, treatment response, and rates of inclusion in clinical research.

Efforts to understand biologic variability and the complex contributions of social determinants of health, disease burden and progression, access to clinical trials, and treatment outcome require careful and diligent study. Approaches for determining and collecting relevant variables for a given disease, condition, diagnostic or therapeutic product, or intervention are necessary.

[110] 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.

3.3 Enhancing diversity and inclusion in the clinical research enterprise serves to advance biomedical science and healthcare and may help reduce health disparities.

Diversity and inclusion in clinical research aims to identify subpopulation variability in diagnosis, treatment, and prevention. Diversity and inclusion also serve to broaden the knowledge base and may identify important group-specific efficacy and safety signals prior to approval of investigational products. Clinical research in which participants reflect the diversity of the intended population for treatment or intervention is better positioned to develop effective treatments for those most likely to use them. A greater understanding of the barriers that negatively impact diversity and inclusion in research is needed so that data supporting future medical innovation better reflect the intended populations of the intervention.

3.4 Appropriate inclusion of diverse populations requires action by, and should become the expectation of, all relevant stakeholders across the continuum of drug development and clinical research involving human participants.

Efforts to achieve enhanced and representative diversity require consideration of complex scientific, organizational, social, and cultural factors, and intrinsic biases. Progress requires engagement, commitment, and accountability by all stakeholders, including sponsors, research institutions, investigators, patients and their advocates, regulatory agencies, oversight bodies and others.

3.5 Refinement in methodology and data analytic tools is necessary to achieve the aims of increased diversity and inclusion.

Development and adoption of common standards, methodologies, and successful strategies will require global collaboration across stakeholders and scientific disciplines and are necessary to advance medicine and public health.

3.6 Advanced and innovative approaches, including use of real world data, may more readily detect differences across groups than can be achieved by individual clinical trials alone.

The size, time, and resource requirements of clinical trials typically preclude their use to detect small but potentially significant differences across all populations of interest. New research paradigms using real world data, curated data sources, machine learning, bioinformatics, and robust analytics are necessary.

4. Suppositions

It is important to emphasize that several tenets ground our analysis, approach, and recommendations, many of which can be inferred from the discussion above:

1. Our recommendations and suggestions should not be interpreted as prescriptive. We are not advocating for "quotas" within each clinical trial or across clinical development programs. We do believe, however, that the general intention of recruitment in research is to reflect the population for which the intervention or research question is directed. We also understand that the right answer to the question of which subgroups to study will likely be "it depends." A **case-based analysis**, examining trade-offs and opportunities, what is already known and unknown, and other factors will drive the choices made. Further, we believe that careful consideration of appropriate inclusion of diverse populations across the research program is essential; the effort must be advertent and intentional to be successful. We have endeavored to present recommendations that are sufficiently **flexible to allow adaptation to the context**, not only of the research question, study design, disease, and epidemiology but also of differing cultures, approaches, and technologies.

2. We believe that both the **scientific understanding of biological diversity** (e.g., "will this product be safe and effective and how generalizable is that determination? What is the heterogeneity of effect?) and **health equity** (e.g., "how will this study help to advance the ability of each person to attain their full health potential?") are both important goals, and that their importance may be weighted differently by different stakeholders. However, the objective of human participant research is generalizable knowledge, and thus the two goals are interdependent and complementary. For example, while the mission of health regulatory authorities is to assure the safety and efficacy of medical products and devices for the general population and not, generally, to weigh social justice concerns in their determinations, considerations of generalizability are directly related to the diversity of the population studied. It is a mistake, therefore, to interpret increasing diversity to reflect the population for which a product is intended as solely a health (or social) equity

effort; it is equally a scientific concern, directed at more accurate understanding of the health effects of any drug, device, biologic or procedure across a broad population.[111]

3. We start from the perspective that **every investigator, sponsor, funder, organization, and participant** should support the goals of diversity and inclusion. We therefore offer recommendations that we believe will further that goal.

4. We believe that **all stakeholders have responsibility** for execution and outcome, although the nature of those responsibilities differ. Further, responsibility is not discharged if certain functions are outsourced to contracted organizations (e.g., academic or for-profit contract research organizations).

5. We hold that the **expectations of inclusion of representative participants in clinical research are applicable to all sponsors and funders of research**. While the drivers and incentives for academic and industry and other sponsors—and the resources available to support the research—may differ, the value of diversity to research does not.

6. When we speak of **diversity** in this document, we mean all the dimensions of diversity: demographic factors (e.g., an individual's sex, gender, race, ethnicity, age, genetic background) and non-demographic factors (pregnancy, metabolism, comorbid conditions, diet, smoking, alcohol use, climate, environment, social determinants of health, local medical practice). We have also tried to draw examples from different dimensions of diversity, although admittedly some are more abstruse than others. When one dimension is particularly relevant, we attempt to make that clear.

7. When we use the term "**social determinants of health**," we accept the definition proffered by the World Health Organization (WHO): "The social determinants of health (SDH) are the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms,

[111] Of note, disproportionate accrual to a study may be required if scientific concerns exist (e.g., it may be necessary to overrepresent—or continue accrual—of a specific subpopulation if early evidence suggests a different safety or efficacy profile).

social policies and political systems."[112] As such, it includes issues such as economic and educational vulnerabilities, sexual orientation, discrimination and other stressors, and additional attributes that, collectively, affect the health status of an individual and their community. We appreciate that more work is needed to understand how SDH impacts clinical research data, medical and behavioral interventions, medicine and public health.

8. We believe in the primary importance of establishing global **standardization of data elements and metadata**, and agreement on **data collection methodologies**. The absence of data and metadata standardization, preferably in a machine-readable format, will hinder progress in data aggregation and analysis.

9. We believe that optimizing inclusion of diverse participants in clinical research requires thought and planning from the earliest conceptualization of the research question and needs an **affirmative commitment** from all stakeholders. **Proactive planning** for recruitment and retention of a diverse population will save time, resources, and costs.

10. **Engagement of patients and participants**, their caregivers and loved ones, patient advocacy groups, and communities throughout the clinical trial lifecycle—from trial design, trial conduct, recruitment, retention, analysis, and return of results—is critically important to optimize the goals of the research, outcomes of relevance to the patient/participant/community, help ensure diverse representation in the trial, and communicate the results. Involvement of individuals, patient organizations, and the community in research implies a continued and long-term commitment by the investigator or sponsor. The optimal goal is a **bidirectional partnership** in which the purpose of the research serves all those engaged.

11. While clinical research may strive to reflect the population that is likely to receive the intervention, in the end what matters is **whether an individual is likely to benefit** from that intervention following its approval and whether the anticipated benefit outweighs the risk of harm. Pre-specified subgroup analyses, if designed to have statistical signifance, may be helpful to differentiate those subpopulations that are predictably high (or low)

[112] World Health Organization,https://www.who.int/social_determinants/en/ [Accessed 22 June 2020]

responders. Results derived from clinical research will always require interpretation for the individual.

12. **New methods and approaches** for appropriate inclusion, represention, data collection, data analysis, and communication are necessary, methods that may involve not only clinical trials but also the integration of observational data, real world evidence, genomic data and other approaches. Investment is necessary until data-driven approaches are found to be effective, and adequate representation, based on evidence, is achieved as a routine expectation of clinical research.

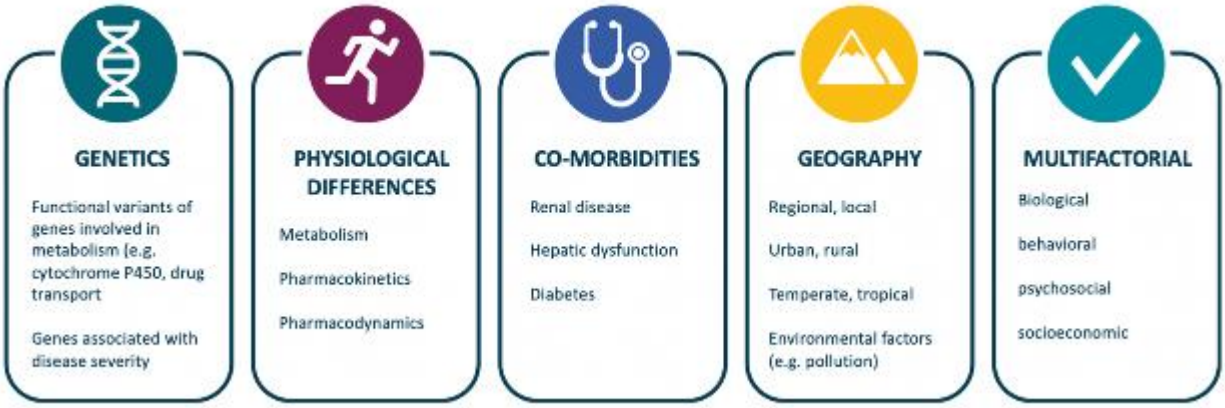
Part B – Background, Ethical Principles, and Regulatory Directives

5. History and Data to Support Diversity Initiatives

5.1 Background Evidence

Complex and interdependent factors, including demographic and non-demographic factors, can lead to variability in drug exposure and/or response from individuals (see Figure 8). The data should be reported with whatever granularity is possible. "Subgroups" may seem to be homogeneous with respect to the outcome of interest, but may actually be composed of greater heterogeneous subgroups with respect to that outcome.

Figure 8: Differences in exposure or response



There are a number of examples that have been well-studied and that provide evidence that treatment outcomes may vary significantly between patient subgroups. For example, the often referenced **African American Heart Failure Trial (A-HeFT)** demonstrated that a fixed combination of hydralazine hydrochloride-isosorbide dinitrate (Bidil) added to standard therapy statistically reduced mortality compared to standard therapy alone in self-identified Black and

African-American patients.[113] That study enrolled only Black patients, a decision based on careful analysis of two prior studies that enrolled a diverse population of patients and that showed potential benefit to Black but not White patients.[114]

The drug development program of the investigative anti-hypertensive medicine **Omapatrilat** (see "Case Study: Omapatrilat" in *Toolkit*), an inhibitor of both neutral endopeptidase and angiotensin-converting enzyme, was terminated because of the safety concern that the development of angioedema was approximately three times more likely to occur in Black participants compared to others.[115]

Eltrombopag is a small-molecule treatment for certain diseases that manifest with a low platelet count, also termed thrombocytopenia. The response to Eltrombopag varies by ethnicity: East Asians (i.e., Japanese, Chinese, Taiwanese, and Korean)[116] have an effective plasma concentration that is 50-55% higher than non-Asians. A lower initial dose (50%), therefore, is recommended for East Asians.[117] The initial dose of eltrombopag is also reduced for patients with hepatic impairment (50%) and, in East Asians, the initial dose is reduced further (25%). Thus both ancestry and organ dysfunction should be considered in prescribing this medicine.[118]

A fourth example involves the antiretroviral drug **Efavirenz** that has been shown to be influenced by underlying genetic variation identified more frequently in specific subgroups.[119]

---

[113] Brody H, Hunt LM. BiDil: assessing a race-based pharmaceutical. The Annals of Family Medicine. 2006 Nov 1;4(6):556-60.
[114] Temple R, Stockbridge NL. BiDil for heart failure in Black patients: The U.S. Food and Drug Administration perspective. Annals of Internal Medicine. 2007 Jan 2;146(1):57-62.
[115] Coats AJ. Omapatrilat-the story of Overture and Octave. International Journal Cardiology. 2002; 86: 1-4.
[116] Novartis, Highlights of prescribing information: Eltrombopag. Revised 7/2017. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/promacta.pdf [Accessed 22 June 2020]
[117] Cheng G. Eltrombopag, a thrombopoietin-receptor agonist in the treatment of adult chronic immune thrombocytopenia: a review of the efficacy and safety profile. Therapeutic advances in hematology. 2012 Jun;3(3):155-64.
[118] Novartis (2017) *op. cit.*
[119] Frasco MA, Mack WJ, Van Den Berg D, Aouizerat BE, Anastos K, Cohen M, Dehovitz J, Golub ET, Greenblatt RM, Liu C, Conti DV. Underlying genetic structure impacts the association between CYP2B6 polymorphisms and response

More generally, one review demonstrated that approximately one-fifth of new drugs approved by the FDA between 2008-2013 found differences in exposure and/or response across racial/ethnic groups that were sufficiently large to result in population-specific prescribing recommendations in a few cases.[120] Some examples of drugs with FDA-approved product labelling language that provide recommendations/precautions aimed at specific races/ethnicities are provided in Table 3.

to efavirenz and nevirapine. AIDS (London, England). 2012 Oct 23;26(16):2097. doi:10.1097/QAD.0b013e3283593602

[120] Ramamoorthy A, Pacanowski MA, Bull J, Zhang L. Racial/ethnic differences in drug disposition and response: review of recently approved drugs. Clinical Pharmacology & Therapeutics. 2015 Mar;97(3):263-73.

Table 3: Selected examples of recommendations provided in the FDA-approved product labeling that are aimed at specific races/ethnicity or ancestry[121]

DRUG	LABELING INFORMATION RELATED TO DIFFERENCES BY RACE/ETHNICITY	JUSTIFICATION
Angiotensin-converting enzyme inhibitor (ACE inhibitors) (e.g., captopril (Capoten®; enalapril (Vasotec®) and others)	A general statement in the labeling that states that ACE inhibitors are associated with a higher rate of angioedema in Black than in non-Black patients. First-line therapy in African-American/Black populations is often less effective than in non-Black patients due to lower renin profile in this population.	The risk of angioedema is ~5 times higher in African-Americans/Blacks. ACE Inhibitors, beta blockers and angiotensin receptor blockers are less effective as a class for hypertension in African-Americans/Blacks because renin-angiotensin-aldosterone is not dominant driver.
Azilsartan medoxomil (Edarbi®) & azilsartan	A general statement in the drug label for azilsartan medoxomil (Edarbi®) states that the effect of	Antiotensin-II receptor blockers can be prescribed as monotherapy or as a combination therapy. Monotherapy is generally less effective in reducing hypertension in

[121] Ramamoorthy A, Pacanowski MA, Bull J, Zhang L. Racial/ethnic differences in drug disposition and response: review of recently approved drugs. Clinical Pharmacology & Therapeutics. 2015 Mar;97(3):263-73.

medoxomil + chlorthalidone (Edarbyclor®)	the monotherapy in reducing blood pressure was approximately half in Black patients. A general statement in the drug label for azilsartan medoxomil + chlorthalidone (Edarbyclor®) states that the blood pressure effect of Edarbyclor in Blacks is similar to that of non-Black patients.	Black/African-American patient populations due to low renin levels, whereas combination therapies (that dually address hypertension and low renin levels) have been found to have a similar effect in Black and non-Black populations.
Carbamazepine (Tegretol®)	A boxed warning in the drug label that describes the risk of serious and sometimes fatal dermatologic reactions (SJS/TEN), a risk higher in people of Asian ancestry. Patients of Asian ancestry should be tested for the presence of HLA-B*1502 allele prior to initiating treatment with this drug.	Studies in patients of Chinese ancestry have found a strong association between the risk of developing Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) and the presence of HLA-B*1502.
Clopidogrel (Plavix®)	Boxed warning for reduced anti-platelet activity in patients with	Less efficacious in persons with CYP2C19*2 or CYP2C19*3 allele, and these allele frequencies are higher

	two loss-of-function alleles in CYP2C19 gene. Detailed description in the pharmacogenomics section of the label describing differing efficacy for different populations with varying allele types.	in East Asians, Native Hawaiians, and other Pacific Islanders.
Isosorbide dinitrate/hydralazine (Bidil®)	This treatment of heart failure was indicated as an adjunct therapy to standard therapy in self-identified Black patients to improve survival and improve patient-reported functional status.	Retrospective analyses suggested an effect on survival in Black patients but showing little evidence of an effect in White patients. Efficacy was confirmed by a trial enrolling only African-American/Black patients.
Rasburicase (Elitek®)	A boxed warning in the label indicating that patients at a higher risk of hemolysis if glucose-6-phosphate dehydrogenase (G6PD) deficient. Patients of African or	This product is contraindicated in patients with G6PD deficiency because of increased risk of hemolysis. G6PD deficiency is commonly seen in patients of African or Mediterranean ancestry.

	Mediterranean ancestry should be screened. Higher risk of methemoglobinemia for unclear reasons.	
Rosuvastatin (Crestor®)	The label suggests starting the drug at a lower initial dosage in Asian populations Elderly appear to be more at risk of myopathy.	Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. Thus, dosage adjustment should be considered in Asian patients.
Tacrolimus (Prograf®)	Based on data in kidney transplant patients, the label indicates that African-American patients required higher doses to attain comparable trough concentrations compared to Caucasian patients.	Higher dose in African-American transplant patients may be due to differential expression of CYP3A4.

Of course, not all differences relate to demographic differences. An important and instructive study termed the Platelet Inhibition and Patient Outcomes (PLATO) trial demonstrated that ticagrelor was more effective than clopidogrel in preventing the composite endpoint of cardiovascular death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) without an increase in overall major bleeding.[122] Importantly, however, of the many prespecified subgroup analyses, there was a significant treatment interaction by geographic region. Further analysis showed that outcomes in patients from the U.S. trended in the opposite direction, favoring clopidogrel, compared with patients from the rest of the world. While the difference in geographic region could have been due to chance alone, subsequent substudies and detailed investigation eliminated differences in baseline patient characteristics, study conduct, and management strategies, and illuminated the cause: the dose of concomitant aspirin explained the treatment-by-geography interaction (p=0.00006).[123] The lowest cardiovascular outcomes were observed in patients treated with ticagrelor and maintenance low-dose aspirin whereas ticagrelor and maintenance high-dose aspirin resulted in the highest event rates, regardless of geographic region. The event rate with clopidogrel was not affected by aspirin dose. Similarly, there are reports of sex differences in drug distribution and response that may affect drug safety and effectiveness, and whether these differences are due to pharmacokinetic, pharmacodynamic, or pharmacogenomic differences, hormonal differences, polypharmacy or other factors are not known.[124]

It is important to realize that differences by geographic region are not necessarily due to baseline patient characteristics (e.g., race or ethnicity, or sex), study conduct, or chance, but may be due to another confounding factor such as standard of care. Whenever geographic differences are observed, further study should be considered.

---

[122] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. New England Journal of Medicine. 2009 Sep 10;361(11):1045-57.

[123] Mahaffey KW, Wojdyla DM, Carroll K, Becker RC, Storey RF, Angiolillo DJ, Held C, Cannon CP, James S, Pieper KS, Horrow J. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation. 2011 Aug 2;124(5):544-54.

[124] Soldin OP, Chung SH, Mattison DR. Sex differences in drug disposition. Journal of Biomedicine and Biotechnology. 2011 Oct;2011.

5.2 FDA Drug Trials Snapshots

As part of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) section 907,[125] the U.S. Congress required the U.S. Food and Drug Administration (FDA) to report on the diversity of participants in clinical trials and the extent to which safety and effectiveness data are based on demographic factors such as gender, age, and race. Recognizing the lack of easily accessible information about participation in drug trials, in 2015 the U.S. FDA Center for Drug Evaluation and Research (CDER) created a transparency initiative termed the Drug Trials Snapshots ("Snapshots"). Snapshots are data available online in a standardized format for a novel drug that is either a New Molecular Entity (NME) or an original biologic product subject to a biologics license application (BLA). Snapshots aggregates the data from participants in the clinical trials that were used to approve the drug or biologic and then stratifies the data by sex, race, age and ethnicity subgroups. Further, Snapshots provide statements on whether there were any observed differences in safety and efficacy by demographic subgroups at the time of approval.

Drug Trials Snapshots data do not include the demographics of the complete drug development program but only of the pivotal trials that were relied upon by the Agency to approve the drug or biologic. It should be noted that Snapshots are published only once for each NME or original biologic and therefore do not include data from subsequent supplemental data including trials of previously approved products being tested for new indications. Additionally, the annual aggregate report represents the data for products approved only in that year and do not correct for diseases that affect only one demographic (e.g., breast cancer, prostate cancer). Thus, if three drugs are approved in any one year for prostate cancer and none for breast cancer, the overall ratio of men versus women may not be representative of the majority of trials. Discriminating review of the data underlying the aggregate report is therefore important.

Over the last five years for which data are available, the overall distribution of demographics by sex and ethnicity appear to be improving, subject to the caveats mentioned below (Table 4). It is noteworthy that the proportion of participants aged 65 and older involved in research

[125] Food and Drug Administration Safety and Innovation Act of 2012. Public Law. 2012:112-144. https://www.govinfo.gov/content/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf [Accessed 27 May 2020]

appears to be variable (Table 4), probably related to the randomness of the "snapshot" of drugs approved in that year.

Table 4: Summary demographic data from Drug Trial Snapshots 2015-2019[126]

	WOMEN	BLACK OR AFRICAN AMERICAN	ASIAN	WHITE	OTHER	AGE 65 AND OLDER
2015	40%	5%	12%	79%	4%	37%
2016	48%	7%	11%	76%	7%	21%
2017	55%	7%	11%	77%	14%	32%
2018	56%	11%	10%	69%	14%	15%
2019	72%	9%	9%	72%	18%	36%

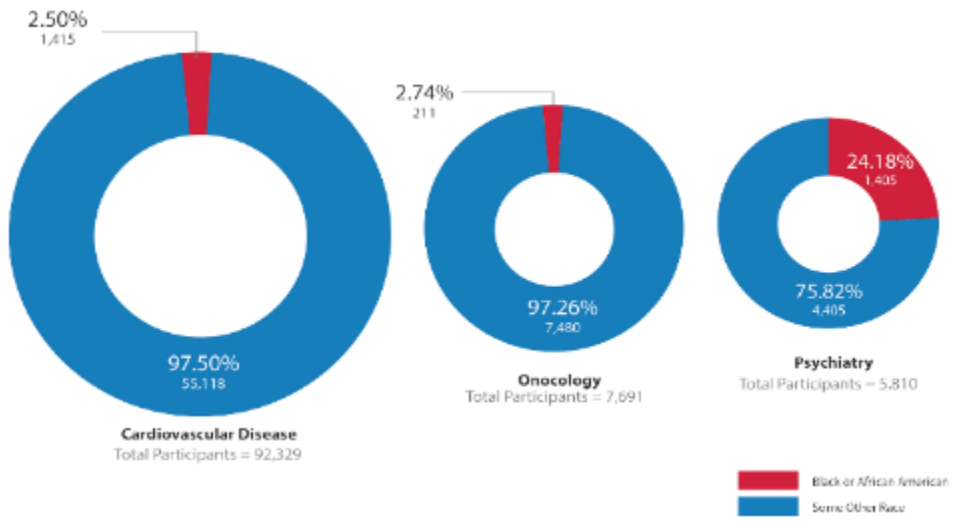
Percentages represent number of participants of a given demographic group as a percentage of all participants in the pivotal trials that led to the marketing decision by the FDA.
Notes: (1) The percentages of the categories "American Indian or Alaska Native (AI/AN)," "Native Hawaiian or Other Pacific Islander (NH/OPI)," and "Unknown/Unreported" were small enough that they are combined into the "Other" category. (2) The demographic "Hispanic" is reported consistently for the first time in 2017.

While summary data are important, they are highly variable. Individual NMEs and biologics vary in the proportions of individuals recruited from outside the U.S. (from 0-100%), of women (from 0-100%, explained in part by disease, e.g., prostate versus breast cancer), and of race and ethnicity. In 2017, Hispanic/Latinx populations were reported independently for the first time and, in the different trials reported, ranged from 0% to 50%. The transparency of the data is important and permits analysis, oversight, and accountability. The data do demonstrate signficiant variability by therapeutic area: in 2015-2016 data, the percent Black or African-

[126] U.S. Food and Drug Administration. Drug Trial Snapshots. Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots. [Accessed 27 May 2020].

Americans in trials of cardiovascular and oncology disease was less than 3%, despite the fact that disease is often more severe, diagnosed later, and of increased mortality in that subgroup. Trials of psychiatric diseases, however, demonstrated participation by 24.2% of Black or African-American patients. The data demonstrate conclusively that recruitment of underrepresented populations is possible. Such data provide a valuable starting point for analysis of approaches to recruitment across different disease entities and settings (Figure 9)**.**

Figure 9: Participation of Black or African American individuals in clinical trials for oncology, cardiology, and psychiatry



From 2015-2016 FDA Global Participation in Clinical Trials Report [127]

The All of Us trial, initiated in May of 2018, has been successful in enrolling over 350,000 participants, of which 80% have been historically underrepresented in biomedical research. (see "Case Study: All of Us Research Program" in *Toolkit*). The All of Us research program is a prospective study of 1,000,000 people or more in the U.S. intending to develop a longitudinal dataset of biospecimens, information (including patient characteristics, environmental and social factors), genetic data, and electronic health record data. Given the diversity in the

[127] 2015-2016 FDA Global Participation in Clinical Trials Report; https://www.fda.gov/downloads/Drugs/InformationOnDrugs/UCM570195.pdf

recruited population, the intention of the study is to further understand how demographic and non-demographic variables, including variables in social determinants of health, affect health and disease.[128]

5.3 Recent media focus and publicity

The lack of diversity in clinical trials continues to sit at the forefront of public media related to health and medicine. A ProPublica analysis published in 2018 highlighted the continued racial disparity in clinical trials, finding that Black and Native American individuals remain under-represented in clinical trials for cancer, despite the incidence of disease being similar between these minority groups and Caucasians. The authors noted that increased attention is needed to focus on access to trials, designing trials with minority communities, and trust-building initiatives (see Section 8.1 "Trust, mistrust and trustworthiness").[129]

We now have an understanding of the importance of diverse representation in clinical trials, but to date an insufficient understanding of the heterogeneity of treatment response. At no time has this problem been more apparent than during the COVID-19 pandemic. Black and Latino, Pacific Islander, and some vulnerable (e.g., homeless, incarcerated, aged) populations have been disproportionately affected by the SARS-CoV-2 virus, and the disease has greater severity and mortality among those populations. This disproportionate impact appears to be related to comorbidities, potential genetic differences, healthcare access, health inequities, exposure risks, among other factors. The fact that we do not have, and generally are not collecting, data to address confounding factors exposes the current, systemic problems we face today. Further, the fact that clinical trials of both treatment and prevention have enrolled largely White populations, despite evidence of the impact of infection on underserved and underrepresented populations, further substantiates the call for change. Only by committing to

[128] All of Us Research Program Investigators. The "All of Us" Research Program. New England Journal of Medicine. 2019 Aug 15;381(7):668-76.
[129] Chen C and Wong R. Black Patients Miss Out On Promising Cancer Drugs. Propublica. 2018 Sept 19. See https://www.propublica.org/article/Black-patients-miss-out-on-promising-cancer-drugs [Accessed 27 May 2020].

inclusion and representation, and then to systematic data collection and analysis, will necessary information be obtained.[130,131 ,132 ,133]

[130] Fontanarosa PB, Bauchner H. Race, ancestry, and medical research. Jama. 2018 Oct 16;320(15):1539-40.
[131] Cooper RS, Nadkarni GN, Ogedegbe G. Race, ancestry, and reporting in medical journals. Jama. 2018 Oct 16;320(15):1531-2.
[132] Nazha B, Mishra M, Pentz R, Owonikoko TK. Enrollment of Racial Minorities in Clinical Trials: Old Problem Assumes New Urgency in the Age of Immunotherapy. American Society of Clinical Oncology Educational Book. 2019 May 17;39:3-10
[133] Abbasi J. Older Patients (Still) Left Out of Cancer Clinical Trials. Jama. 2019 Nov 12;322(18):1751-3.

6. Application of Ethical Principles to Aims of increasing Diversity in Clinical Research

The MRCT Center's Diversity Framework draws upon the three principles fundamental to the ethics of clinical research. These ethical principles support the approaches set forth in the MRCT Center's Diversity Workgroup Guidance and *Toolkit*.

6.1 Respect for persons

The ethical principle of respect for persons is borne out of the idea that all individuals have agency and autonomy and retain the right to make voluntary informed decisions.[134] Recognizing that not all persons are capable of self-determination, respect for persons also requires that we protect those with diminished autonomy. In response to a long history in which captive, decisionally-impaired, and otherwise vulnerable individuals were exploited in the name of science, a shift to protection, often at the expense of inclusion, characterized research with women of childbearing potential, the aged, children, the cognitively impaired, those of lower socioeconomic class, and others. [135] According to the Belmont Report, "to show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment *when there are no compelling reasons to do so*."[136] The wholesale exclusion of categories of individuals can be seen as denying access to those who could potentially benefit from research and who, in turn, can benefit research by expanding our understanding of biological variability among sub-groups. Remedies to common impediments to the enrollment of diverse populations recognize that respect for persons

[134] This right of self-determination of course extends beyond the clinical research setting to choices regarding treatment and care.
[135] 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.
[136] 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.*Emphasis added.*

requires efforts to reach, engage, and inform traditionally excluded populations about research in a manner that addresses their intellectual, language, and cultural needs.

6.2 Beneficence

The ethical principle of beneficence creates an obligation to maximize the benefits of research while minimizing its harms, an obligation that applies to the research enterprise as a whole and includes investigators and study staff, IRBs, sponsors, contract research organizations (CROs), funders, and others. The benefits of research can be understood as involving those that accrue directly to the individual research participant and also to society at large. Diversity and inclusion are responsive to the obligation required of beneficence along a number of dimensions. First, diversity promotes generalizability by maximizing the evidence base that informs new treatment approvals. Second, inclusion of previously understudied groups may provide specific information regarding treatment response, tolerability, and adverse events in specific subgroups. Third, understudied and underserved populations may benefit directly from access to the investigational treatment protocol. Finally, diversity in research participation may ultimately serve to promote greater equity in healthcare. As discussed in Chapter 14 "The Role and Responsibility of the IRB/REC in Inclusion and Equity," about a role for the IRB in accountability, the inclusion of individuals at either end of the age range, with comorbidities, and those otherwise uniquely susceptible to risk may serve to increase the generalizability of the research, but may also introduce risks to the participants. For example, the inclusion of participants with comorbidities can provide important clinical information about safety and efficacy in that population, but additional laboratory monitoring during the course of the trial may be necessary to identify and avoid adverse events.

6.3 Justice

The concept of justice is applied to human research in the Belmont Report as the equitable distribution of benefit and burden (or risk) across society. A long history of research involving participants selected because they were susceptible to manipulation, such as the poor or uneducated, and individuals living in institutions such as prisons, orphanages, and psychiatric hospitals, gave rise to the idea that "research should not unduly involve persons from groups

unlikely to be among the beneficiaries of subsequent applications of the research."[137] In the aftermath of the problems identified in the Tuskegee Study of Untreated Syphilis in the Negro Male,[138] the Willowbrook State School experiment in which intellectually disabled patients were intentionally infected with the hepatitis virus,[139] and Dr. Southam's experiments injecting cancer (HeLa) cells into unknowing patients at the Jewish Chronic Disease Hospital,[140] the application of justice focused on protection of potential participants, and often of those seen as particularly vulnerable. Protectionism favored exclusion of groups seen as at increased risk or unable to give voluntary informed consent. This stance had unwanted consequences for the study of certain subgroups, limiting their inclusion in research even when scientifically appropriate. More broadly, justice requires the equitable distribution of the benefits of research, and those who do not participate cannot be its beneficiaries.[141] In this way, justice and fairness in the distribution of the benefits of clinical research demand the inclusion of diverse populations not only for the potential individual benefit of participation but, more importantly, to inform the evidence base upon which regulatory and medical coverage decisions are made.

[137] 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.
[138] Reverby SM. Examining Tuskegee: The infamous syphilis study and its legacy. Univ of North Carolina Press; 2009.
[139] Rothman DJ. Were Tuskegee & Willowbrook'studies in nature'?. Hastings Center Report. 1982 Apr 1:5-7.
[140] Levin AG, Custodio DB, Mandel EE, Southam CM. Rejection of cancer homotransplants by patients with debilitating non-neoplastic diseases. Annals of the New York Academy of Sciences. 1964 Nov;120(1):410-23.
[141] And see Weijer C. Selecting subjects for participation in clinical research: one sphere of justice. Journal of medical ethics. 1999 Feb 1;25(1):31-6.

7. Existing Regulations and Guidance

Many international guidance documents and national regulations address whether, when, and how to include diverse populations in clinical research, both during investigational product development and post-approval studies. Some guidance has been published globally that addresses issues relevant to the inclusion of diverse populations in clinical research. The International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) focused on the impact of ethnicity on a medicine's effect,[142] considerations for special populations,[143,144] and multi-regional clinical trials.[145] In addition, the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), published and periodically updates the "International Ethical Guidelines for Health Related Research involving Humans,"[146] containing guidance pertinent to diverse inclusion.

[142] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline. Ethnic factors in the acceptability of foreign clinical data E5(R1). 5 February 1998. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E5_R1/Step4/E5_R1__Guideline.pdf [Accessed 1 August 2020]

[143] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline. Studies in Support of Special Populations: Geriatrics E7. 24 June 1993. Available at: https://database.ich.org/sites/default/files/E7_Guideline.pdf [Accessed 2 August 2020].

[144] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline. Clinical Investigation of Medicinal Produces in the Pediatric Population E11(R1). 18 August 2017. Available at: https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf. [Accessed 2 August 2020].

[145] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Guideline. General principles for planning and design of multi-regional clinical trials E17. Finalized 16 November 2017. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E17/E17EWG_Step4_2017_1116.pdf. [Accessed 1 August 2020]

[146] Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO). International Ethical Guidelines for Health Related Research involving Humans. Available at: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf. [Accessed 27 May 2020]

While regulation around this issue exists in the United States,[147,148] Canada,[149] and Australia,[150] less directive guidance exists in other countries. A remarkable resource for international regulations is the National Institute of Allergy and Infectious Diseases (NIAID) ClinRegs online database for comprehensive country-specific clinical research regulatory information that provides links to relevant official regulations and guidance.[151] While countries may not have regulation or guidance specifically to address diversity and its role in clinical research, available regulatory material dealing with research on special populations may be relevant.

It is impossible to review all relevant guidance, regulation and law here. Select representative documents are discussed in Table 5. We encourage the submission of additional references,[152] and we will update the document and/or table with the receipt of additional information.

[147] Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA). Public Law 112-144. 112th Congress. July 9, 2012. Available at: https://www.govinfo.gov/content/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf. [Accessed 27 May 2020].
[148] U.S. Code of Federal Regulations. 42 § 289a–2, as amended: July 1, 1944, ch. 373, title IV, § 492B, as added Pub. L. 103–43, title I, § 131, June 10, 1993, 107 Stat. 133; amended Pub. L. 114–255, div. A, title II, §§ 2031(c), 2038(b), 2053, Dec. 13, 2016, 130 Stat. 1056, 1065, 1076. Available at: https://www.govinfo.gov/content/pkg/USCODE-2011-title42/pdf/USCODE-2011-title42-chap6A-subchapIII-partH-sec289a-2.pdf and as amended by the 21st Century Cures Act at: https://www.govinfo.gov/content/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf (p1064ff). [Accessed 27 May 2020]
[149] CIHR Guidelines for Health Research Involving Aboriginal People (2007-2010) - CIHR. (2020). Retrieved 6 February 2020, from https://cihr-irsc.gc.ca/e/29134.html [Accessed 27 May 2020]
[150] National Statement on Ethical Conduct in Human Research (2007) - Updated 2018. Available at https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018 [Accessed 27 May 2020]
[151] Consult https://clinregs.niaid.nih.gov/ [Accessed 27 May 2020]
[152] Please send additional information to MRCT@bwh.harvard.edu

Table 5: Global regulation and guidance for diverse inclusion in clinical research

ISSUING BODY	GUIDANCE/REGULATION	DIRECTIVE FOR DIVERSE INCLUSION
INTERNATIONAL		
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)	ICH-E5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data A Medicine's Sensitivity to Ethnic Factors (1998)	Provides guidance for considering the impact of ethnic factors on a medicine's pharmacokinetics, pharmacodynamics and therapeutic effects. The impact of ethnic factors upon a medicine's effect will vary depending upon the drug's pharmacologic class and indication and the age and gender of the patient.
	ICH E7: Studies in Support of Special Populations: Geriatrics (1993)	Provides recommendations for studies directed principally toward New Molecular Entities that are likely to have significant use in the elderly or diseases that specifically affect the elderly (e.g., Alzheimer's Disease). In addition, there are questions and answers specifically addressing this population.
	ICH E11 and ICH E11(R1): Clinical Investigation of Medicinal Products in the Pediatric Population (2017)	These guidelines focus on scientific and technical issues of pediatric clinical trials, regulatory requirements for planning pediatric studies, and the necessities of conducting complex trials in pediatric populations. Dimensions that differ by age are considered as are formulation, toxicity, and excipient standards.

	ICH E17: General Principles for Planning and Design of Multi-Regional Clinical Trials (2017)	Provides guidance on general principles on planning/designing Multi-Regional Clinical Trial (MRCT). Because regulatory agencies evaluate data from MRCTs conducted globally, a harmonized international guideline was thought necessary to facilitate data acceptance. Focusing on scientific issues, ICH E17 is intended to complement the guidance provided in the ICH E5(R1) Guideline and facilitate MRCT.
Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO)	International Ethical Guidelines for Health Related Research involving Humans (published 2016)	CIOMS presents an ethical guideline for research in human participants, entitled "International Ethical Guidelines for Health-Related Research involving Humans," last published in 2016 and periodically updated. The document contains several specific guidelines related to diversity in clinical research.
UNITED STATES		
Food and Drug Administration (FDA)	Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA). Sec. 907	Provides a directive to investigate how well demographic subgroups, including sex, age, race and ethnicity, in applications for medical products, drugs, biologics and devices, submitted to the agency for marketing approval: 1) are included in clinical trials; and 2) have data available for subgroup-specific safety and effectiveness.
	Enhancing the Diversity of Clinical Trial Populations –	Provides recommendations and approaches that sponsors of clinical trials can use to

	Eligibility Criteria, Enrollment Practices, and Trial Designs	support a new drug application or a biologic license application to broaden eligibility criteria when scientifically and clinically appropriate and increase enrollment of underrepresented populations in their clinical trials.
	Collection of Race and Ethnicity Data in Clinical Trials	Provides recommendations on the use of a standardized approach for collecting and reporting race and ethnicity in clinical trials for regulated medical products conducted in the U.S. and abroad.
	Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies	Provides recommendations for the evaluation and reporting of age-, race-, and ethnicity-specific data in medical device clinical studies and aims to improve the quality, consistency and transparency of data regarding the performance of medical devices.
United States Congress	U.S. 42 § 289a–2.Inclusion of women and minorities in clinical research, and as amended by the 21st Century Cures Act	Provides regulation ensuring inclusion of women and minority populations in clinical research, regardless of cost. The 2016 amendment clarified age subgroups (including pediatric) to be considered and emphasized need for research on sexual and gender minorities.
	U.S. FDA Reauthorization Act of 2017 (FDARA) Sec. 610.	In 2017, FDARA was signed into law. Section 610 of FDARA required FDA to convene a public meeting to discuss clinical trial eligibility criteria to inform guidance on the

	Pub. L. No. 115-52, 131 STAT.1005 (2017)	subject. The Duke-Margolis Center for Health Policy and FDA held a public workshop in 2018. A report titled Evaluating Inclusion and Exclusion Criteria in Clinical Trials [153] was published 90 days after the public meeting.
GLOBAL		
European Medicines Association (EMA)	**Europe**: Guideline on the investigation of subgroups in confirmatory clinical trials (published 2019)	This document offers guidance for assessors in European regulatory agencies on assessing subgroup analyses in confirmatory clinical trials that are presented in a Marketing Authorization Application. The document recognizes that variability in response to treatment between patients can be caused by "demographic, environmental, genomic or disease characteristics, comorbidities, or by characteristics related to other therapeutic interventions."
National Health and Medical Research Council (NHMRC), The Australian Research Council (ARC) and	**Australia:** National Statement on Ethical Conduct in Human Research 2007 (updated 2018)	This document was jointly developed by the National Health and Medical Research Council (NHMRC), The Australian Research Council (ARC) and Universities Australia (UA). It provides "guidelines for researchers, Human Research Ethics Committees, and others conducting ethical review of research; and emphasizes institutions' responsibilities for the quality, safety, and ethical acceptability of research that they sponsor or permit to be carried out under their auspices." Section 4, explicitly

[153] Evaluating Inclusion and Exclusion Criteria in Clinical Trials; Workshop Report; Availability. (2018). Retrieved from https://www.federalregister.gov/documents/2018/08/23/2018-18232/evaluating-inclusion-and-exclusion-criteria-in-clinical-trials-workshop-report-availability [Accessed 22 June 2020]

Universities Australia (UA)		discusses ethical considerations specific to participants.
Health Canada	**Canada:** Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences (published 2013)	Provides operational guidance on the "study and analysis of sex differences in clinical trials of therapeutic products in order to generate evidence to advise on the optimal use of therapeutic products in both women and men."
Canadian Institute of Health Research (CIHR)	**Canada:** Canadian Institute of Health Research (CIHR) Guidelines for Health Research Involving Aboriginal People	Provides guidance to promote health through research in alignment with Aboriginal values and traditions. The purpose of the guideline is to help develop research partnerships to facilitate and support mutually beneficial and culturally competent research.
Brazil National Health Council (CNS)	**Latin America**: Resolution 304 (updated 2000)	Provides ethical guidelines for conducting clinical research on indigenous populations in Brazil.
	Asia: National Ethical Guidelines for Biomedical	Provides ethical guidelines for conducting clinical research and justifies

Indian Council of Medical Research (ICMR)	and Health Research on Human Subjects (published 2017)	inclusion/exclusion on a number of vulnerable populations in India.
South Africa Department of Health	**Africa:** Ethics in Health Research: Principles, Processes, and Structures (published 2015)	Provides ethical guidelines for conducting clinical research on a number of vulnerable populations, including minors, in South Africa.

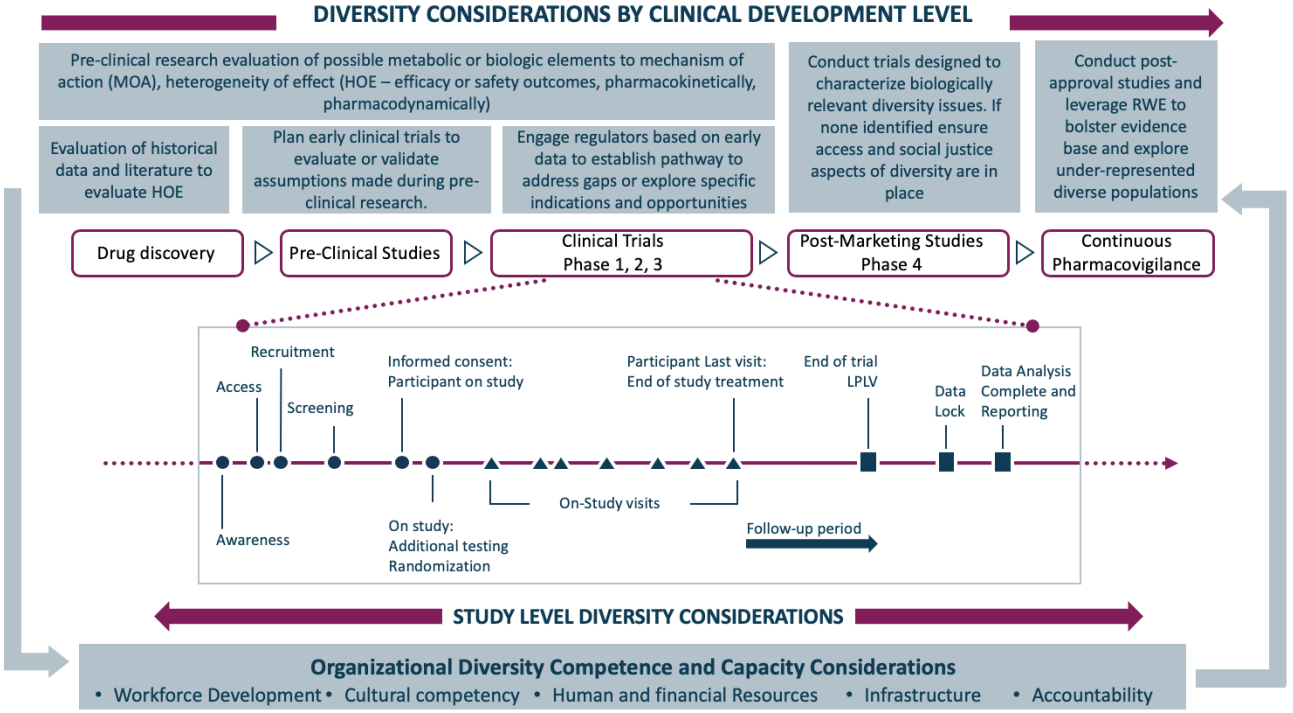
Transition from Parts A and B to Parts C to E

In Part A and B of this guidance, we have discussed a number of theoretical considerations, and some of the regulatory and ethical guidance, that support diverse representation and inclusion in clinical research. In Part C to E of this guidance, we consider the practical barriers that have been identified or hypothesized to prevent routine participation of underrepresented, underserved, and diverse populations; further, we propose potential solutions or remedies to overcome those barriers. Recommendations for each barrier are presented, some of which involve time, resources, and a change in general practice.[154] Importantly, a broad approach to the solutions specific to the situation, and particularly to the communities and populations of interest, should be considered and endorsed, and any solution set should examine every area of product development, approval, and later, post-approval studies. We describe the multiple interacting dimensions between organizational, product development, and study level interventions throughout Parts C, D, and E (see Figure 7).[155] We note that given the intersecting barriers and potential remedies, the separation of chapters and sections is somewhat arbitrary, but we attempt to organize and describe the importance of each. Making inroads is likely to require humility, receptivity to open communication, research, and partnership, as the solution set will not be uniform. We will only make progress if conversation and exploration is encouraged and endorsed.

[154] In addition to the Recommendations located at the end of each section, the MRCT Center has developed a Diveristy *Toolkit* to offer a comprehensive set of free tools, checklists and logic models for download and modification.

[155] The MRCT Center developed a series of logic models to visually present practical approaches to these complex considerations (see "Introduction to Logic Model" in *Toolkit*). The "Overall Logic Model for Parts C, D, & E of the Guidance Document" (see *Toolkit*) presents a high-level, systematic approach to Broadening Engagement, Data Variable and Analysis, and Study Design, Conduct and Implementation. Please note, the logic model was created as a guidance model and may not include all the necessary strategies related to a single specific protocol.

Figure 7: Product development pathway (This figure is repeated here for ease of reference.)



Traditional product development includes interacting considerations of diversity that span throughout drug development - from early drug discovery, pre-clinical research, clinical trials development, and to post-marketing approval and pharmacovigilance. From the start of drug discovery and pre-clinical studies, widespread evaluation for mechanisms of action (MOA) and potential heterogeneity of effect (HOE) need to be prioritized to inform further research and development. At the clinical study level, and throughout all trial phases, organizations need to consider and proactively plan for recruitment and retention of a diverse study population that are reflective of potential heterogeneity of prevalence, or effect/outcomes. Organizations should consider putting in place checkpoints and mechanisms to assess assets diversity planning as they progress through stage-gates (from pre-clinical to early clinical and at phase 1/2 transition for example) that diversity is a consideration for effective planning. Simultaneously, organizations need to consider the competence of their workforce and capacity of the organization to appreciate and emulate the importance of diversity and inclusion within the organization and its product portfolio.

Part C first considers **participant and community engagement**. Clinical interventions are intended to improve the diagnosis, treatment, or prevention of disease and to promote health; for that, it is important to encourage the active engagement of patients and participants, their families and caregivers, advocacy groups and the community, and community health care providers. We then consider **workforce development**, as professional development (e.g., training, education, cultural understanding) of the current workforce is necessary, as are prioritizing professional development and opportunities for a more diverse workforce.

Part D considers issues of **data standards, data collection and reporting, and data analysis**, specifically focusing on diversity and subgroup identification and analysis.[156]

In **Part E**, we move to issues relating to the **study protocol and conduct**, including the importance of the product lifecycle, research question, study design, eligibility (inclusion/exclusion) criteria, recruitment plans, feasibility assessments, recruitment and retention issues, the logistics of the study conduct and associated payments as well as the **role and responsibilities of IRBs/RECs** in conducting ethical review and oversight

Promoting diverse representation and inclusion in clinical research is a shared responsibility by all in the research enterprise.

[156] No study can be designed without a clear definition of data variables, nor executed without data collection methods defined. Data analysis occurs only after study completion. Here, however, we present data analysis immediately after data standards and data collection, only to avoid redundancy.

Part C – Broadening Engagement

8. Participant and Community Engagement

KEY SUMMARY

- Authentic partnerships between and among patients and participants, their caregivers, patient advocacy groups, community-based organizations (e.g., YMCAs, youth centers), cultural and faith-based organizations, places of worship, and non-profit organizations, on the one hand, and with investigators, research teams, sponsors, clinicians, and clinical research sites on the other, are necessary for research programs to be responsive to the needs of affected populations and successfully to recruit and retain underrepresented and underserved populations.

- Understanding the community and its priorities requires long-term investment in effort, time, and resources by investigators, research teams, clinical research sites and sponsors. It involves investigators, research teams, clinical research sites and sponsors—either themselves or through an intermediary—being part of and understanding the community. Generally, the community relationships are more effective when they are not built or based on specific project needs but are part of a long-term strategy of engagement and dialogue.

- Meaningful engagement of underserved and underrepresented patients and their communities requires an openness to their perspectives and values. While there is no single formula, success derives from efforts that include patients and their communities in research planning and decision-making and through diversification of the workforce, advisory processes, and formal consultations.

- Building trust requires engagement with patients/participants and their caregivers founded upon the pillars of mutual respect and support.

- Treating physicians and providers in the community, community health workers, formal and lay social workers and other key people in specific communities—who often have the trust of patients and potential participant—are important partners in research.

Participant, patient, caregiver, and community[157] engagement influence and can improve the design and execution of clinical research, including efforts to enhance diversity and inclusion. Appropriate and meaningful engagement offers opportunities for outreach to individuals and communities including those underrepresented or underserved in research, to address priorities that are important for patients and potential participants, and to draw upon the perspectives of the very individuals for whom the research is intended. There is increased acknowledgement by clinical trial sponsors, researchers, and patient groups that patients and communities should be involved in decision-making and the design of studies.[158] Progress can be accelerated by a concerted effort among investigators and their research teams, sponsors, clinicians, and others to develop and implement long-term, consistent, and bi-directional partnerships focused on active engagement with patients, potential participants and communities (see "Introduction to Logic Model," "Logic Model: Participant and Community Engagement" and "Participant and Community Engagement Potential Key Performace Indicators" in *Toolkit*).

It is important to appreciate that direct engagement of patients, caregivers, and families can be complementary to that of patient advocacy groups and community-based organizations. It is sometimes difficult to determine when sufficient "patient input" has been captured, as individual patients and participants have their own unique perspectives, concerns, and burdens that need to be respected, but this should not deter sponsors from gathering patient

[157]Throughout Part C - Broadening Engagement, we use selected terms to refer to different sets of individuals. The following definitions are applied for general clarity:
- *Patient*: a person who has, may have, or is at risk for a condition and that may be a candidate to participate in clinical research;
- *Potential participants:* individuals not yet involved in a research study yet able to contribute perspective and insight on the applicability and acceptability of the research;
- *Participant*: individuals screened for or on a clinical trial;
- *Caregivers*: persons who assist and care for the patient or participant, including loved ones, guardians, etc.
- *Public*: inclusive of persons or members of the population(s) without a condition
- *Community*: a group of people living in the same place or sharing common characteristics, inclusive of potential and current patients and participants
- *Stakeholders:* individuals or groups of individuals interested in or concerned about a given topic

[158] Sacristán JA, Aguarón A, Avendaño-Solá C, Garrido P, Carrión J, Gutiérrez A, Kroes R, Flores A. Patient involvement in clinical research: why, when, and how. Patient preference and adherence. 2016;10:631-640.

perspectives. There are cultural differences as well that can be addressed (see Section 10.1 "Cultural considerations").

It is important to underscore one note of caution. When investigators or sponsors interact *directly* with participants and/or individuals, particularly those affected by rare and ultrarare diseases, miscommunication and mistaken expectations may sometimes result. For instance, a patient or family member may believe that a trial "spot" has been guaranteed, or that they will have continued access to experimental therapy when the trial has ended or terminated. Further, knowing the eligibility criteria for entry and/or the endpoints of a trial in advance may introduce unconscious bias. Communication should be clear, and often substantiated in writing, to avoid misunderstanding, false hope, or the promise of treatment or apparent benefit.

8.1 Trust, mistrust and trustworthiness

Lack of trust in research, investigators, and the research "system," and fear of being treated as a "guinea pig," are major barriers to clinical research participation. Trust and trustworthiness of the profession (professionals, researchers, healthcare system) by the individual and the public are important considerations during communications and collaborations between researchers and participant/community groups. The development of communications and partnerships with trusted individuals and community groups (providers, community leaders, faith-based community organizations, etc.) in a manner that is effective, transparent, respectful and culturally appropriate helps build trust.[159]

Engagement requires genuine respect and support— for patients and participants and their representative communities—and demonstrates interest, concern, and compassion.[160] Patients, participants, and communities should be seen and treated as important partners in research, and should know what they deserve and should expect from the partnership and from research. The commitment to engagement can lead to an open, curious and responsive dialog among investigators, sponsors, and participants, fostering trust and creating value.

[159] Warren RC, Shedlin MG, Alema-Mensah E. Clinical trials: African American leadership interviews. Executive version of the literature and findings; 2017. Available at: http://tuskegeebioethics.org/wp-content/uploads/2018/01/55762_Clinical-Trial-2_DM_NO_CROPS_WEB.pdf [Accessed 22 June 2020

[160] Frosch DL, Tai-Seale M. R-E-S-P-E-C-T—What it Means to Patients. *J Gen Intern Med* 2014: 29, 427–428. https://doi.org/10.1007/s11606-013-2710-z

When preparing to work with potential participants and communities from disparate backgrounds (race, ethnicity, sex, gender, nationality, etc.), investigators and research teams should assess their own implicit bias[161] around working with populations different than those with whom they self-identify.[162] Self-awareness can provide helpful, if sometimes difficult, insights.[163] Understanding of implicit bias can promote receptivity to different viewpoints, especially of the people the research ultimately aims to serve.

Further, it is important to establish consistent, meaningful engagement with patient communities to build trust and promote bi-directional discussion.[164] Meaningful engagement implies recognizing the complexity and distinctiveness of individuals, families and communities; participating in social groups and events to become part of and to understand the community; asking how to serve the community; and staying connected over time.

Patient and community engagement will lead to a process of co-creation. One should anticipate how to discuss, construct, and agree upon clear and mutual expectations around roles and responsibilities, starting from the research and development process, through publication and dissemination. Ideally, the clinical protocol would be subject to co-development; if, however, this were not possible, then unbiased feedback from patients and potential participants should be sought. A willingness to adjust outcome measures for relevance to the patient population should be anticipated and considered.[165] A common concern of both researchers and patients, however, is that the communication and reciprocity will be replaced by the false appearance of

[161] Harvard University. Project Implicit [internet]. 2011 [cited 03 March 2020]. Available from: https://implicit.harvard.edu/implicit/takeatest.html
[162] FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. *BMC Med Ethics* 18, 19 (2017). https://doi.org/10.1186/s12910-017-0179-8
[163] Repetitive implicit bias training may be helpful as individuals may experience and learn from the trainings differently at different times. It may also reinforce organizational values and priorities.
[164] Shippee ND, Domecq Garces JP, Prutsky Lopez GJ, Wang Z, Elraiyah TA, Nabhan M, Brito JP, Boehmer K, Hasan R, Firwana B, Erwin PJ, Montori VM, Murad MH: Patient and service user engagement in research: a systematic review and synthesized framework. Health Expect. 2013, doi: 10.1111/hex.12090
[165] Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. Patient related outcome measures. 2018;9:353.

inclusiveness.[166,167] An appreciation—and acknowledgement—of the power asymmetry that exists between researchers and patients, and between researchers (or sponsors) and communities is important especially for those individuals and communities that have historically been marginalized.

Whoever directly interacts with patients and communities should clearly communicate how the rights and interests of participants will be protected. The sharing of all information (e.g., informed consent process, education around research procedures, disease management, aggregate trial results) should be done in a health-literate manner that is both clear and honest. Crafting the informed consent document and accompanying discussion is a good example of a situation in which an engaged participant population can provide input, guidance, and help in translating information so it is meaningful for the audience. A research team can seek guidance from current and former participants and patients to optimize consent. That input and guidance are equally applicable to assent materials and discussions with children, and with participants who are decisionally-impaired, and for electronic forms of consent. Importantly, it is the responsibility of the communicator to be understood, not a burden on or expectation of the audience receiving the communication. Skill in clear communications that includes not only plain language but also numeracy, visualization, design, and cultural competence and humility,[168] is an important property of respect. It is important to assess and establish fluency in the language of the clinical research site and documents—which may be other than English in non-U.S. settings—or provide translation and interpretation. Generally in settings within the U.S., Spanish translations should be made available. To the extent possible, it is the responsibility of the researcher to make sure that the protocol is available in the languages of the study participants.

Below, we first consider patients, caregivers, and families, and the role of patient advocacy groups; we then follow with considerations for community partnership and engagement.

---

[166] Domecq JP, Prutsky G, Elraiyah T, Wang Z, Nabhan M, Shippee N, Brito JP, Boehmer K, Hasan R, Firwana B, Erwin P. Patient engagement in research: a systematic review. BMC health services research. 2014 Dec;14(1):89. https://doi.org/10.1186/1472-6963-14-89

[167] Smith YR, Johnson AM, Newman LA, Greene A, Johnson TRB, Rogers JL: Perceptions of clinical research participation among African American women. 2007, 16 (3): 423-428.

[168] Hook JN, Davis DE, Owen J, Worthington Jr EL, Utsey SO. Cultural humility: Measuring openness to culturally diverse clients. Journal of Counseling Psychology. 2013 Jul;60(3):353.

8.2 Patient and patient advocacy engagement

Clinical trial sponsors and researchers benefit from the involvement of patients and patient groups early in and throughout the development and design of clinical trials, engaging patients as partners and co-creators to inform the drug-development process[169] and later, when approved products are subject to additional clinical research. From the earliest time of study conceptualization and design, patients, their caregivers and families, and patient advocacy groups can advise on and address patient values and preferences when selecting relevant study endpoint(s), identifying outcomes that are applicable to their lived experience.[170] Further, they can provide practical advice on reducing the burden of participation, including the number and location of study procedures, provision of childcare resources, reimbursement for participation, and other logistical expectations, and by evaluating patient-facing materials. Patients and patient advocacy groups can facilitate outreach to and inclusion of a diverse population of participants, particularly if the patients, caregivers, advocates, and associated groups reflect the diversity of the intended trial population (e.g., racial and ethnic minorities; sex and gender considerations; primary language; urban/rural locations).[171]

There are numerous examples of success. In the U.S., the Patient-Centered Outcomes Research Institute (PCORI) since its inception, has involved patients in the assessment and prioritization of research and has required active patient engagement in every study. PCORI cites, as its mission, "promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community."[172] Indeed, merit review criteria for grant applications include a measure for patient centricity and for patient

[169] Greenhalgh T, Hinton L, Finlay T, Macfarlane A, Fahy N, Clyde B, Chant A. Frameworks for supporting patient and public involvement in research: Systematic review and co-design pilot. Health Expectations. 2019 Apr 22.
[170] For instance, someone with rheumatoid arthritis may care more about an endpoint that assesses whether a treatment restores the ability to care for oneself (e.g. activities of daily living) than changes on a radiographic image.
[171] Tackling Representativeness: A Roadmap and Rubric. National Health Council. 2017. https://www.nationalhealthcouncil.org/sites/default/files/Representativeness%20in%20Patient%20Engagement.pdf [Accessed 22 June 2020]
[172] Patient-Centered Outcomes Research Institute (PCORI) Our Vision and Mission. Available at: https://www.pcori.org/about-us/our-vision-mission [Accessed 22 June 2020]

and stakeholder engagement (see PCORI Merit Review Criteria[173]. As one example of the hundreds of projects funded (see PCORI search engine),[174] PCORI provided an award to a project focused on improving the consent process for clinical research using public input and deliberation in diverse communities, with a focus on teens who were part of sexual and gender minorities.[175] In the U.K., the James Lind Alliance[176] has established a process, termed "Priority Setting Partnership (PSP)" that enables patients, caregivers, and clinicians to agree on priorities for future clinical research and has instituted measures to ensure that patients are systematically participating in the research process. Similarly, the Canadian Institute of Health Research has established a strategy for patient-oriented research to foster patients as partners, focusing on patient-identified priorities and improving outcomes.[177] These and many other efforts have been undertaken to improve patient-centricity in the clinical research ecosystem, and while these examples have focused on national and federal programs, many other programs exist (see Figure 10). This work appropriately demands sustained commitment and partnerships; lessons can be learned,

Figure 10: Examples of patient-focused efforts

- Count Me In (https://joincountmein.org/)
- Patient Groups & Clinical Trials (https://www.ctti-clinicaltrials.org/projects/patient-groups-clinical-trials)
- Patient Focused Medicines Development (https://patientfocusedmedicine.org/pfmd-member-benefits/)
- Savvy Cooperative: Ask Patients (https://www.savvy.coop/)

[173] Patient-Centered Outcomes Research Institute (PCORI) Merit Review Criteria. Available at https://www.pcori.org/funding-opportunities/merit-review/merit-review-criteria [Accessed 22 June 2020]
[174] Patient-Centered Outcomes Research Institute (PCORI) Explore Our Portfolio of Funded Projects. https://www.pcori.org/research-results?f%5B0%5D=field_project_type%3A298 [Accessed 22 June 2020]
[175] *Use of Public Deliberation in Diverse Communities to Improve Consent Processes for Clinical Research*. (2019). *Pcori.org*. Retrieved from https://www.pcori.org/research-results/2019/use-public-deliberation-diverse-communities-improve-consent-processes-clinical [Accessed 22 June 2020]
[176] *The James Lind Alliance | James Lind Alliance*. (2019). *Jla.nihr.ac.uk*. Retrieved from http://www.jla.nihr.ac.uk/ [Accessed 22 June 2020]
[177] *Canada's Strategy for Patient-Oriented Research - CIHR*. (2019). *Cihr-irsc.gc.ca*. Retrieved 31 October 2019, from http://www.cihr-irsc.gc.ca/e/44000.html#a4.1 [Accessed 20 October 2019]

adapted and enhanced toward diversity both from community-based participatory research[178] and other co-creation models.[179]

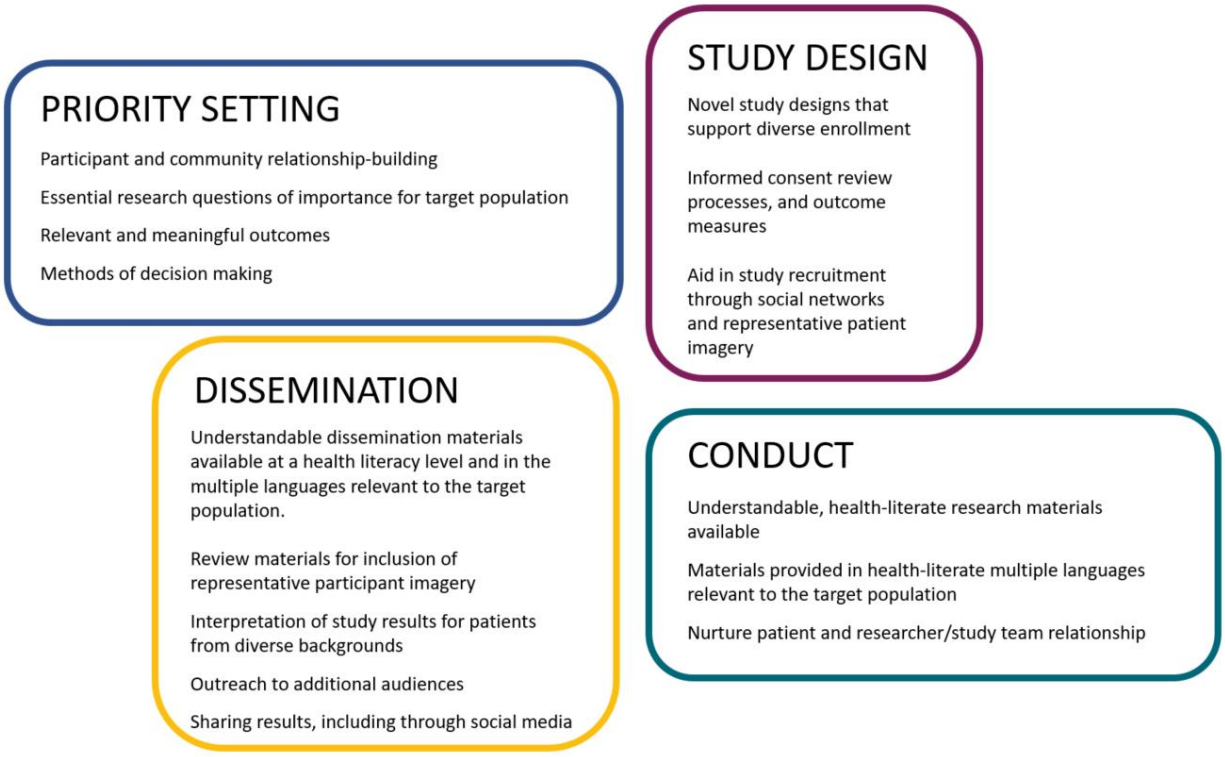
Several frameworks have been formulated around patient involvement in research. A systematic review by Greenhalgh et al[180] provides five broad taxonomies that describe different frameworks to address patient engagement. As described in that review, these include power-focused, priority-setting, study-focused, report-focused, and partnership-focused. The "*power-focused*" frameworks centers on revealing, surveying, and overcoming the investigator-participant power differentials. "*Priority-setting"* frameworks focus on the patients' involvement in setting research priorities. "*Study-focused"* frameworks aim to expand recruitment and retention in clinical trials to advance the quality and effectiveness of research for social good. The "*report-focused'* frameworks involves how patient and public involvement was managed in clinical research. Finally, the "*partnership-focused*" frameworks aim to ensure transparency and public accountability in the academic/sponsor and participant/community relationships. While each framework has a theoretical underpinning and each has specific strengths and limitations, they are complementary and advance the implementation and feasibility of patient engagement in research.

While appreciating the theory of patient engagement is helpful, having a planned, dynamic, and iterative strategy to involve potential participants, patients, patient advocacy groups, and communities (see Section 8.3 "Community engagement" and "Case Study: Multiple Sclerosis Research Mythbusting Series" in *Toolkit*) in co-creation and conduct of clinical research is important. The strategy does not need to be created anew for each trial but can be adapted from established, successful practices, and should be considered as part of the clinical development plan. We recommend that the strategy include elements from each stage of the

[178] Kwon SC, Tandon SD, Islam N, Riley L, Trinh-Shevrin C. Applying a community-based participatory research framework to patient and family engagement in the development of patient-centered outcomes research and practice. Translational behavioral medicine. 2017 Nov 29;8(5):683-91.
[179] Woolf SH, Zimmerman E, Haley A, and Krist AH. Authentic engagement of patients and communities can transform research, practice, and policy. Health Affairs. 2016; 35(4), 590-594. https://doi.org/10.1377/hlthaff.2015.1512
[180] Greenhalgh T, Hinton L, Finlay T, Macfarlane A, Fahy N, Clyde B, Chant A. Frameworks for supporting patient and public involvement in research: Systematic review and co-design pilot. Health expectations: an international journal of public participation in health care and health policy. 2019; 22(4):785-801.

clinical trial, including priority setting, study design, conduct, and dissemination (see Figure 11 and "Diverse Participant Engagement Strategies: A Checklist" in *Toolkit*).

Figure 11: Application of patient engagement strategies across four different stages of research



Consultation and partnership with patient advocates need to be practical and actionable, and therefore the representatives should be chosen thoughtfully. Representatives, often accessed through patient advocacy groups, must understand that recommendations in study question, design, and conduct will be applied to all participants, so the level of customization has to be reasonable.

8.3 Community engagement

Research must serve the public good. To do so, it should be informed by the specific priorities of populations affected by the condition being studied and their communities.[181] Community advocates have an awareness of relevant issues, and in minority communities they can provde insights into historical and cultural considerations to help remedy mistrust and barriers to participant enrollment and retention.[182] Community engagement[183] of minority populations may further help to promote outreach, acceptance, and implementation of research findings that, in turn, may improve health outcomes and contribute to reduced disparities. For effective community engagement, investigators and research teams should invest in, be part of, and/or have an understanding of the community that the research is intended to serve.[184] There is no single formula for this process.[185] A few examples of ways to engage with communities are included in Figure 12. Establishing these sustainable relationships creates value and trust in the long term; ideally, the

Figure 12: Ways to engage with communities

- Engage minority healthcare physicians and staff
- Engage those who are self-identified with the community at issue, including minority PIs and study staff
- Attend community events
- Establish a presence at community centers and clinics by offering free health screenings

[181] Holzer JK, Ellis L, Merritt MW. Why we need community engagement in medical research. Journal of Investigative Medicine. 2014; 62(6), 851-855.
[182] Clark B, Tepp R. Community engagement is key to clinical trial recruitment and diversity. STAT, 28 Aug. 2019, https://www.statnews.com/2019/08/23/clinical-trial-recruitment-diversity-community-engagement/ [Accessed 22 June 2020]
[183] The Centers for Disease Control and Prevention defines community engagement as "…the process of working collaboratively with and through groups of people affiliated by geographic proximity, special interest, or similar situations to address issues affecting the wellbeing of those people. It is a powerful vehicle for bringing about environmental and behavioral changes that will improve the health of the community and its members. It often involves partnerships and coalitions that help mobilize resources and influence systems, change relationships among partners, and serve as catalysts for changing policies, programs, and practices"(CDC, 1997, p. 9).
[184] Holzer JK, Ellis L, Merritt MW. Why we need community engagement in medical research. Journal of Investigative Medicine. 2014; 62(6), 851-855.
[185] Kimminau KS, Jernigan C, LeMaster J, Aaronson LS, Christopher M, Ahmed S, Boivin A, DeFino M, Greenlee R, Salvalaggio G, Hendricks D. Patient vs. community engagement: emerging issues. Medical care. 2018 Oct;56(10 Suppl 1):S53.

community should view the research endeavor as a partnership, not as something done "to" or "upon" them. Ideally, research is or will be viewed as a "public good" aimed at addressing issues that are important to and impactful for all communities, including minoritiy communities. For this effort to be efficacious, entities that interact with the community should make a long-term commitment, and not engage the community for their single study or purpose, only to relinquish the community partnership upon completion of the study. Effective partnerships that reflect the diversity of the community are aided by, and sometimes considerably reliant upon, specific key individuals who have strong personal relationships with many different stakeholders and stakeholder groups and who perform both formal and informal networking and "translation" work.

Holzer et al.[186] outlined three different case examples of sustainable community engagement practices that center on building trust, encouraging participation, and promoting dissemination and understanding of the results of the research. Figure 13 is an adaptation of the specific approaches utilized by the authors; incorporating approaches that use one or more of these activities can enhance engagement efforts.

[186] Holzer J K, Ellis L, Merritt MW. Why we need community engagement in medical research. Journal of Investigative Medicine. 2014: 62(6), 851-855.

Figure 13: Process, approach and strategy for community engagement

8.4 Case examples of community engagement initiatives

- EMD Serono, the biopharmaceutical business of Merck KGaA in Darmstadt, Germany, formed a collaboration with the Accelerated Cure Project (ACP) for Multiple Sclerosis and its iConquerMS people-powered research network to obtain and integrate the views of people affected by Multiple Sclerosis (MS) into the design and implementation of its clinical trials, particularly to develop relevant patient-reported outcomes (PROs) endpoints.

- Sanofi implemented Patient Advisory Panels to obtain input on aspects of planned clinical trials from the perspective of potential participants. The 2019 global priorities for Research and Development included patient advisory panels to help inform research." (For detailed information refer to "Case Study: Diverse Patient Engagement at a Pharmaceutical Company" in *Toolkit.)*

- Takeda frames its description of "who we are" on its public website with the statement:[187]

  "How can we do more for our patients?
  Everything at Takeda starts with this question."

  The company supports that statement with a team dedicated to patient engagement, helping to ensure that patients and the patient community perspectives are incorporated into the development of new medicines.

- The Yale Center for Clinical Investigation (YCCI) established a partnership with The African Methodist Episcopal Zion (AME Zion) Church, New Haven's oldest African American congregation, and Junta for Progressive Action, New Haven's oldest Latinx community-based non-profit, to facilitate a direct link between the local community and investigators. (For detailed information refer to "Case Study: Diverse Recruitment at Yale Center for Clinical Investigation" in *Toolkit.*)

- Eli Lilly and Company partnered with The Center for Drug Development and Clinical Trials at Roswell Park Cancer Institute to create an innovative, first of their kind, pharmaceutical sponsored, workshop series to train minority physicians to become clinical trial investigators. The workshop series sought to develop a broader base of diverse investigators who understand the principles of good clinical trial design and have the tools to conduct trials that are relevant to underrepresented populations. With a goal to increase the diversity of clinical trial participants, this workshop series contributed to creating a more robust approach to clinical research.

- Collaborating with the Center for Information and Study on Clinical Research Participation (CISCRP) and the National Minority Quality Forum, Biogen is committed "to increasing patient engagement and education around diversity in clinical trial participation."[188] In addition, they formed a cross-functional internal team of Biogen employees to support the effort.

[187] Takeda Who We Are. https://www.takeda.com/who-we-are/ [Accessed 2 March 2020]
[188] Biogen. Building Trust and Diversity in Clinical Trials. Available at: https://www.biogen.com/en_us/yearinreview/spotlight_003.html. [Accessed 17 May 2020]

8.5 Recommendations

RECOMMENDATIONS
ALL
• Develop training for principal investigators, study staff, and others on implicit bias, as it may affect relationships between and among stakeholders, (see Project Implicit https://implicit.harvard.edu/implicit/takeatest.html – Harvard University). • Understand the rights that research participants, their loved ones and advocacy groups have to be treated with respect, to ask and receive answers to any questions pertaining to the study, to be free from any pressure to participate in the study, to decline to be in the study, and to change one's mind about continued participation in the study at any time. • Recognize the rights of patients include the right to be informed and to be contacted to be asked to participate. A central challenge is that patients are not informed, nor asked, by their own healthcare providers to assess their interest in clinical research participation. • Engage principal investigators, study staff, participants, participant advocacy organizations, and communities from diverse backgrounds, which requires sustained commitment and partnership. If a sponsor, healthcare system, research site, or investigator is unable to sustain the participant, it would be appropriate to engage a trusted intermediary (e.g., community health center, community group) that has been involved in and is able to commit to the community. • The most effective community engagement, intersects with a community's broader life, not just its health and medical challenges. Look for ways to support and participate that bring members of the research community into public events, celebrations, and appropriate informal activities
SPONSORS, ACADEMIC MEDICAL CENTERS, CLINICAL RESEARCH SITES, AND INVESTIGATORS AND THEIR STUDY TEAMS
• Establish a process for the involvement of underserved and underrepresented participant voices in the clinical research design phase, appreciating the diversity of

opinion and perspectives (refer to Figure 13 for steps on how to initiate community engagement).

- Form a sustaining partnership with patient advocacy groups and community organizations to promote the value of research by forming community advisory boards, patient advisory boards, patient interviews, patient screening simulations, or other means (refer to Figures 11 and 13).
- Facilitate structured in-person or virtual meetings with the patient community or patient advocacy organizations to discuss topics including: study design elements, informed consent forms, study communication and branding, patient recruitment and study materials, logistical modifications, and technological solutions.
- Obtain patient and advocate review of all participant-facing materials (e.g., information sheets, research-related directions and instructions, informed consent documents, plain language summaries for return of aggregate results).
- Discuss program-level decisions (e.g., disease focus, drug development program) of indications, eligibility criteria, outcomes, and endpoints with the intended patient population, incorporating the input to the extent possible.
- Co-create the study question and design with patients, patient advocacy groups, and community members, recognizing that trials also need to support and comply with expectations by health regulatory authorities.
- Reimburse or compensate participants and patient advocacy organizations appropriately for time and expenses (including travel and services) incurred while advising on program development or trial design without compromising their independence. Online and remote participation in these discussions should be considered when possible.
- Establish expectations and terms of referral with investigators and clinical research sites (e.g., frequency of communications, expected research-related study procedures that can be accomplished locally, return of participant to referring physician on completion of trial, information in advance of and following trial termination).
- Be patient, expect there to be some miscommunications and misunderstandings, plan for bumps in the road, and remain committed to the process.

HEALTHCARE PROVIDERS

- Utilize training on cultural competence (emphasizing knowledge and skills) and cultural humility (emphasizing attitudes).
- Be empowered to negotiate with sponsors, academic medical centers, and investigators on their expectations and terms of referral to investigators and clinical research sites (e.g., frequency of communications, expected research-related study procedures that can be accomplished locally, information in advance of and following trial termination, return of participant to the healthcare provider on completion of trial.)

PATIENTS, COMMUNITY ORGANIZATIONS AND THE PUBLIC

- Understand the logistical requirements (e.g., time, transport, assistance) of the research protocol and what is needed for successful participation by participants, caregivers, community organizations, and the public.
- Understand whether research-related procedures can be accomplished locally (e.g., at a local clinic or by a visiting nurse) or virtually (e.g., using mobile technologies) to avoid visits to a study site.
- Understand whether information concerning study-related results will be provided to the participant and/or the community, and when relevelant, whether participant will receive their individual study results and from whom.
- Understand whether personal data or samples will be shared or used for any other purpose than the research, and whether that data or sample will identify individuals.
- Understand whether the treatment being tested in the study will be available at the end of a clinical trial if the participant is benefitting from it.
- Know whether the participant will need to pay for any part of the study.
- Know what will happen as a result of any injury that occurs because the research.
- Advise on the language and format of any participant materials (e.g., informed consent document, instructions for research procedures) to help ensure health literate clear communication.

9. Participant Awareness, Knowledge and Access

KEY SUMMARY

- A potential participant's awareness, knowledge, and access are intersecting elements that impact the researcher, participant, and community engagement in clinical research.
- Early planning to establish presence in communities and to develop researcher-participant-community relationships and partnerships will directly improve participant awareness, knowledge and access (see Chapter 8 "Participant and Community Engagement").
- Awareness initiatives to increase diversity in clinical research are more successful when a multipronged approach is used and linked through community engagement.
- Knowledge and understanding of clinical research is an essential pre-requisite for continued participant involvement. Thus it is important to use educational materials that emphasize topics relevant to patient care, and educational interventions. These should be offered periodically to improve participant comprehension of relevant clinical research items.
- Participation in clinical research depends upon patients feeling supported, informed, listened to, understood, and welcomed throughout the research study. An important element is understanding the patient's emotional and practical support system, and whether this comprises family members, friends, faith community, or others. While these others may not appear in clinic with the patient, their support should not be undervalued.
- Empirical data demonstrate that there is no difference among subpopulations in willingness or ability to participate. Study participation is significantly influenced by who is *invited* to participate, and therefore special attention must be placed on choice of study site and on implicit bias of research staff.

A potential participant's awareness, knowledge, and access to an appropriate clinical trial are essential, intersecting factors that influence participation in and successful representation of a diverse participant pool in a clinical trial. A trial cannot be successfully completed on time, on

budget, and with appropriate representation without first establishing a connection between researchers and the people who may want to participate in the research.[189] Only after awareness, knowledge and access to a clinical trial are established[190] can a willingness to participate be evaluated. This "willingness to participate" is often referenced as one of the reasons that ethnic and racial minorities are poorly represented in clinical research.[191,192,193] Some empirical data exist, however, suggesting that, among individuals exposed to clinical research, Black participants are equally willing to participate as White participants.[194,195] Although these data may have limitations, the studies suggest that (1) previous exposure (and thus knowledge of the clinical trial process) is valuable and (2) access to, referral for, and recommendation for participation are important. Cultivating a connection between the research community and participating community is a critical step that requires early, diligent, and careful planning well before a research question is created (See Chapter 8 "Participant and Community Engagement"). This chapter reviews strategies and approaches aimed at increasing awareness, knowledge,[196] and access among underserved and underrepresented participants. Efforts to promote potential participants' awareness, knowledge, and access to clinical trials is complemented by a workforce that understands and communicates effectively to patients; effective workforce development is described in Chapter 10 "Workforce and Diversity: Training and Development."

---

[189] Jerome RN, Dunkel L, Kennedy N, Olson EJ, Pulley JM, Bernard G, Wilkins CH, and Harris PA. To end disease tomorrow, begin with trials today: Digital strategies for increased awareness of a clinical trials finder. Journal of Clinical and Translational Science. 2019 3: 190–198.

[190] Brown M, Moyer A. Predictors of awareness of clinical trials and feelings about the use of medical information for research in a nationally representative U.S. sample. Ethnicity & health. 2010 Jun 1;15(3):223-36.

[191] Katz RV, Green BL, Kressin NR, Claudio C, Wang MQ, Russell SL. Willingness of minorities to participate in biomedical studies: confirmatory findings from a follow-up study using the Tuskegee Legacy Project questionnaire. J Natl Med Assoc 2007;99(9):1050–62.

[192] Davis JL, Bynum SA, Katz RV, Buchanan K, Green BL. Sociodemographic differences in fears and mistrust contributing to unwillingness to participate in cancer screenings. J Health Care Poor Underserved 2012; 23:67–76

[193] Rivers D, August EM, Sehovic I, et al. A systematic review of the factors influencing African Americans' participation in cancer clinical trials. Contemp Clin Trials. 2013; 35(2):13–32.

[194] Durant RW, Legedza AT, Marcantonio ER, Freeman MB, Landon BE. Willingness to participate in clinical trials among African Americans and whites previously exposed to clinical research. J Cult Divers. 2011;18:8-19. PMID: 21526582; PMCID: PMC3241443.

[195] Wendler D, Kington R, Madans J, Van Wye G, Christ-Schmidt H, et al. (2006) Are racial and ethnic minorities less willing to participate in health research? PLoS Med 3(2): e19.

[196] In this regard, health-literate, searchable registries of open clinical trials are or would be of value, including those maintained by patient advocacy organizations, foundations, and government entities. See for example CISCRP "Search Clinical Trials," available at: https://www.ciscrp.org/services/search-clinical-trials/. [Accessed 22 June 2020].

A potential participant's *awareness* is the understanding that research exists in order to develop generalizable knowledge about the diagnosis, treatment, and prevention of disease and the promotion of human health; *knowledge* relates to understanding the purpose of the research, what it means for one's overall treatment (if applicable), and the potential opportunity it may provide to other patients or communities; and *access,* from a potential participant's perspective, is the extent to which clinical trials or research studies are made available to an individual (see Figure 14).

Figure 14: Awareness, knowledge, access

Awareness: Understanding that research exists for general and specific clinical conditions or medical situations

Knowledge: Understanding the purpose of research

Access: The extent clinical trials or research studies are made available to an individual

Awareness and knowledge are often interconnected, and existing literature indicates that patients of racial and ethnic minority are less aware of clinical trials.[197] They are therefore perceived to be less knowledgeable about the benefits from participating in clinical research, and the way that medical data can be used in advancing research.[198,199,200,201] The literature suggests that various factors—ranging from logistical burdens like schedule conflicts, lack of transportation, and childcare, to psychological issues such as mistrust emanating from historical abuses of respect for persons in clinical research—are the commonly reported barriers that impact minorities' willingness to participate in research. That concept has been challenged,

[197] Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggly S. Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. Cancer Control. 2016 Oct;23(4):327-37.
[198] Wendler D, Kington R, Madans J, Van Wye G, Christ-Schmidt H, Pratt L, Brawley O, Gross C, Emanuel E. Are Racial and Ethnic Minorities Less Willing to participate in health research? PLOS Med. 2006 Feb; 3(2): e19.
[199] Rivers D, August EM, Sehovic I, et al. A systematic review of the factors influencing African Americans' participation in cancer clinical trials. Contemp Clin Trials. 2013; 35(2):13–32.
[200] Durant RW, Wenzel JA, Scarinci IC, Paterniti DA, Fouad MN, Hurd TC, Martin MY. Perspectives on barriers and facilitators to minority recruitment for clinical trials among cancer center leaders, investigators, research staff, and referring clinicians: enhancing minority participation in clinical trials (EMPaCT). *Cancer*. 2014 Apr 1;120 Suppl 7(0 7):1097-105.
[201] Winter SS, Page-Reeves JM, Page KA, Haozous E, Solares A, Nicole Cordova C, Larson RS. Inclusion of special populations in clinical research: important considerations and guidelines. *J Clin Transl Res*. 2018 Apr 7;4(1):56-69.

however, by a systematic review[202] of survey data from 70,000 individuals—the majority of whom were from the U.S., Europe, Australia and New Zealand—that found no difference between race or ethnicity and willingness to participate, as determined by consent rates. Notably, for an individual to consent, he or she must be *asked* to participate or invited to consider participating. It is not uncommon for researchers to assume that ethnic, racial or other minority groups will not wish to participate in research (see Section 10.2 "Training of clinicians and the importance of study teams") and therefore do not approach or consider them. Simply put, study participation and the demographics of participating individuals are significantly influenced by who is *invited* to participate,[203,204] and support the observations discussed above that when invited to participate, there is no difference in willingness or ability to participate. Translating awareness into knowledge and understanding about clinical research for a patient, family or community requires more than just knowing that the research exists – it requires facilitators to help navigate, distill, and explain such information. These facilitators may include social support groups, clinicians, family members, friends, patient navigators,[205] and community health workers.[206,207] Overall, awareness-raising initiatives to enhance diverse representation in

[202] Wendler D, Kington R, Madans J, Van Wye G, Christ-Schmidt H, et al. (2006) Are racial and ethnic minorities less willing to participate in health research? PLoS Med 3(2): e19.
[203] Wendler D, Kington R, Madans J, Van Wye G, Christ-Schmidt H, Pratt L, Brawley O, Gross C, Emanuel E. Are Racial and Ethnic Minorities Less Willing to participate in health research? PLOS Med. 2006 Feb; 3(2): e19.
[204] Mody L, Miller DK, McGloin JM, Freeman M, Marcantonio ER, Magaziner J, Studenski S. Recruitment and Retention of Older Adults in Aging Research: (See editorial comments by Dr. Stephanie Studenski, pp 2351–2352). Journal of the American Geriatrics Society. 2008 Dec;56(12):2340-8.
[205] Patient navigators provide a bridge between patients and the health care system by enhancing understanding, communication, education and providing other facilitative services to patients. Ghebre RG, Jones LA, Wenzel JA, Martin MY, Durant RW, Ford JG. State-of-the-science of patient navigation as a strategy for enhancing minority clinical trial accrual. Cancer. 2014 Apr 1;120:1122-30.
[206] Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggly S. Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. Cancer Control. 2016 Oct;23(4):327-37.
[207] Winter SS, Page-Reeves JM, Page KA, Haozous E, Solares A, Nicole Cordova C, Larson RS. Inclusion of special populations in clinical research: important considerations and guidelines. *J Clin Transl Res*. 2018 Apr 7;4(1):56-69.

Figure 15: Initiatives to promote awareness and knowledge of clinical research

- Community outreach days to develop a presence within a community
- Successful partnerships with local organizations (e.g. non-governmental organizations [NGOs], libraries, places of worship)
- Relationship building with community clinics, clinicians, and healthcare providers
- Providing educational material at local schools, community centers, and churches
- Media campaigns (e.g. mailing flyers, advertisements on radio, podcasts, social media, billboards)

clinical research are more successful when a multipronged approach is used[208] and linked through communities and social partnerships (see Figure 15 and "Awareness Raising Initiatives to Promote Diverse Participant Engagement" in *Toolkit*).[209] These awareness-raising efforts should first focus on general information about clinical research rather than on one specific trial; it is essential that the public understands the role and function of clinical trials and of clinical research before anyone is asked to participate. Research Participant Resources,[210] sponsored by Harvard Catalyst, for instance, is a useful public resource that provides free downloadable brochures with basic information on clinical research and research procedures for providers, participants, and communities; each is translated into 16 languages (see Figure 16).[211] The Center for Information and Study on Clinical Research Participation (CISCRP) has a suite of general informational materials[212] available, as do many patient advocacy groups and others.[213] Once this broad awareness of clinical research has been

[208] Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggly S. Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. Cancer Control. 2016 Oct;23(4):327-37.
[209] Otado J, Kwagyan J, Edwards D, Ukaegbu A, Rockcliffe F, Osafo N. Culturally competent strategies for recruitment and retention of African American populations into clinical trials. Clinical and translational science. 2015 Oct;8(5):460-6.
[210] Research Participant Resources - Harvard Catalyst. (2020). Retrieved from https://catalyst.harvard.edu/services/rsa/ [Accessed 2 July 2020]
[211] Witte E, Winkler SJ, Myerson J, Kirby A, Biggers J, Do JM, Roth MT, Gateman AK, Cagliero E, Bierer BE. Development of a plain-language library of educational resources for research participants. Journal of clinical and translational science. 2018 Feb;2(1):27-30.
[212] CISCRP Education Center. Available at: https://www.ciscrp.org/education-center/. [Accessed 16 May 2020].
[213] The MRCT Center, for instance, produced a series of "Should I join?" one-page information sheets in the setting of the https://mrctcenter.org/blog/resources/covid-19-clinical-research-flyers/ COVID-19 pandemic. Available at: https://mrctcenter.org/blog/resources/covid-19-clinical-research-flyers/ [Accessed 4 July 2020]

addressed with the community overall, efforts can pivot toward more targeted awareness-raising activities for specific trials.

Figure 16: Health-literate information for research participants is available in 16 languages

Access to a trial adds another layer of complexity. Access is the ability of a person to participate or contribute to the research trial or study. Trial design and logistical accommodations can facilitate *physical access* to a trial through site selection and location (e.g., urban versus rural settings, reimbursement for travel and ancillary expenses, etc.), infrastructure and physical accessibility (e.g., facilities that are accessible for persons who are physically disabled, language translation of materials and signage), and through alternative trial designs (e.g., decentralized clinical trials, hybrid trials that involve home visits, mobile health technologies) (see Chapter 13

"Study Protocol and Conduct"). Access, however, extends beyond physical and structural considerations into *psychosocial and interpersonal factors*[214] Access to participation in clinical research depends not only on physical considerations and proximity to a clinical site, but also on enabling the patient to feel supported, understood, and welcomed.[215]

Recently, knowledge and access to clinical research trials has shifted toward a more patient-centric focus with the development of virtual and hybrid clinical trials (see Section 13.2 "Study question and design") that optimize participant convenience without compromising data integrity. One small benefit of the COVID-19 pandemic and the requirement for social distancing has been the increased adoption of and tools to support virtual trials. In addition, search portals, such as ClinicalTrials.gov, ResearchMatch.com, TrialsToday,[216] CISCRP "Search Clinical Trials,"[217] and advocacy and patient groups that assist in locating appropriate trials assist the community in finding trials that may be appropriate for them. Further, social media is used as a knowledge and recruitment tool.[218,219] Not only is technology improving trial visibility and improving access, but stakeholders are encouraging trial enrollment and participation through more centralized mechanisms such as online participant portals and phone applications. For example, the National Cancer Institute (NCI) created a central participation mechanism, the Cancer Trials Support Unit (CTSU), to make its cancer trials more available to the public.[220] Currently, about 87% of actively enrolling treatment trials sponsored by NCI utilize the CTSU, and in 2018, more than 40,000 individuals were linked to an appropriate

[214] Wendler D, Kington R, Madans J, Van Wye G, Christ-Schmidt H, Pratt L, Brawley O, Gross C, Emanuel E. Are Racial and Ethnic Minorities Less Willing to participate in health research? PLOS Med. 2006 Feb; 3(2): e19.
[215] McDougall, G.J., Jr., Simpson, G., & Friend, M.L. (2015). Strategies for Research Recruitment and Retention of Older Adults of Racial and Ethnic Minorities. Journal of Gerontological Nursing, 41(5), 14–23.
[216] Jerome RN, Dunkel L, Kennedy N, Olson EJ, Pulley JM, Bernard G, Wilkins CH, Harris PA. To end disease tomorrow, begin with trials today: Digital strategies for increased awareness of a clinical trials finder. Journal of clinical and translational science. 2019 Aug;3(4):190-8.
[217] CISCRP "Search Clinical Trials," available at: https://www.ciscrp.org/services/search-clinical-trials/. [Accessed 22 June 2020].
[218] Gelinas L, Pierce R, Winkler S, Cohen IG, Lynch HF, Bierer BE. Using social media as a research recruitment tool: ethical issues and recommendations. The American Journal of Bioethics. 2017 Mar 4;17(3):3-14.
[219] Caplan A, Friesen P. Health disparities and clinical trial recruitment: Is there a duty to tweet?. PLoS biology. 2017 Mar;15(3).
[220] Available online: https://www.ctsu.org/Public/Default.aspx?ReturnUrl=%2f [Accessed 22 June 2020]

cancer trial through the portal.[221] The *Fox Trial Finder,*[222] created by the Michael J. Fox Foundation for Parkinson's disease, enables people with Parkinson's disease, as well as control participants, to find clinical trials focused on developing treatments.

Figure 17: Community relationship building and the use of "Cultural Ambassadors"

After receiving a recommendation from a community member at a focus group discussion, the Yale Center for Clinical Investigation (YCCI) developed its own "Cultural Ambassador" program to help recruit minorities into clinical research studies. The ambassadors were tasked with forming partnerships with local churches and community-based non-profit organizations (for the full case study, see "Case Study: Diverse Recruitment at Yale Center for Clinical Investigation" in Toolkit). Since implementing this program, YCCI has seen a dramatic shift in minority participation rates. In fact, participation rates of historically underrepresented populations in studies at YCCI that involve Cultural Ambassadors has not dropped below 12%. In fiscal year 2018, 30% of all accrued enrollment across Yale studies were historically underrepresented populations. These impressive results of community engagement demonstate that recruitment of minority and underserved

Efforts to increase access for minority and other underrepresented populations to clinical research requires all stakeholders to be conscious of potential bias, to engage clinical sites accessible to those populations, to invite underserved individuals to participate, to identify and preempt challenges to their participation, and to provide solutions to common factors that may inhibit participation, (e.g., adjustment of scheduled clinic hours, provision of child or elder care, arranging for participant travel, and reimbursement of travel expenses, meals, other out-of-pocket costs, or lost wages associated with the trial, see Section 13.5.2 "Study conduct and retention"). Overcoming barriers to awareness, knowledge, and access represents a long-term commitment of sponsors, investigators, healthcare institutions, patients, advocacy groups, and government institutions. Long-term commitment

[221] Finnigan, S. Cancer Trials Support Unit (CTSU) Contract Renewal Proposal. Presentation. 25 March 2019. National Cancer Institute. Online: https://deainfo.nci.nih.gov/advisory/bsa/0319/Finnigan.pdf [Accessed 22 June 2020]
[222] FOX TRIAL FINDER : Parkinson's Disease Clinical Trials . (2020). Retrieved from https://foxtrialfinder.michaeljfox.org/ [Accessed 22 June 2020]

will improve communication and credibility, thereby building trust and understanding among all stakeholders in the research enterprise. It is important to remember that commitment requires time, planning, anticipation that difficulties will arise, and patience.

A key factor to improving awareness, knowledge and access to clinical trials for underrepresented populations is finding effective methods of engagement and information transfer specific to the situation, including identifying organizations and trusted individuals within the communities. Working with communities is one successful means to enroll and retain members of minority groups in clinical research. For example, see Figure 17 "Community relationship building and the use of 'Cultural Ambassadors.'"[223,224,225]

[223] Hughson JA, Woodward-Kron R, Parker A, Hajek J, Bresin A, Knoch U, Phan T, Story D. A review of approaches to improve participation of culturally and linguistically diverse populations in clinical trials. Trials. 2016 Dec 1;17(1):263.
[224] McDougall GJ, Simpson G, Friend ML. Strategies for research recruitment and retention of older adults of racial and ethnic minorities. Journal of gerontological nursing. 2015 Mar 30;41(5):14-23.
[225] Mody L, Miller DK, McGloin JM, Freeman M, Marcantonio ER, Magaziner J, Studenski S. Recruitment and Retention of Older Adults in Aging Research: (See editorial comments by Dr. Stephanie Studenski, pp 2351–2352). Journal of the American Geriatrics Society. 2008 Dec;56(12):2340-8.

9.1 Recommendations

RECOMMENDATIONS

For Sponsors, Investigators, Providers and Healthcare Institutions

- Engage with the community to establish community presence (See Chapter 8 "Patient and Community Engagement").
- Commit to long-term partnerships with local trusted organizations and/or trusted intermediaries that provide sustained connectivity to the community.
- Appreciate the value of obtaining community insight and perspectives on what is important to community members and how those issues should be addressed.
- Develop specific educational programs and other resources to support research literacy and to help bridge knowledge/awareness gaps, particularly for newly diagnosed patients.
- Implement broad clinical research education programs in engaged communities, using materials from educational institutions and/or in collaboration with them.
- Educate community members on specific trials (prior to recruitment notice), which is a necessary prerequisite to participation.
- Consider dedicated recruitment coordinators for research sites who can travel to public locations (e.g., health fairs, free clinics) to educate about clinical trials; consider funding for this work through the clinical trial budget.
- Consider financial needs of the community partner, and include these needs in grant funding applications if necessary.
- Include in the study budget reimbursement, compensation, and, possibly, incentives for the participant (and an accompanying person, if necessary) beyond a stipend.
- Treat community engagement as bi-directional: sponsors, investigators, and research study teams should not "visit" a community with an "ask" without expecting to be responsive, and potentially give of themselves, in return.

For Patients, Community Organizations, and the Public

- Make patients aware of the current lack of diversity in clinical trials that can limit clinical decision making – i.e., "if patients like you are not in clinical trials, we have no data on how these drugs or devices will work for you and your family, and this limits our ability as physicians to make recommendations."
- Increase the involvement of patient advocacy organizations in promoting diverse inclusion of participants in clinical research and providing awareness materials for the public regarding the benefit of clinical research.

10. Workforce and Diversity: Training and Development

KEY SUMMARY

- A clinical research workforce should be trained in the skills necessary to support, understand, and communicate with a culturally diverse participant population.
- Clinicians and healthcare providers need to be educated on the role of clinical research in establishing the safety and effectiveness of diagnostic, therapeutic, and preventive interventions in order to explain the research to their patients and encourage their participation; the need to understand bias and to learn ways to modify behaviors; approaches to enroll and retain diverse populations; and the potential opportunities of participation.
- Important educational resources to clinicians and healthcare providers include information related to:
    - Clinical research
    - The availability of actively enrolling trials, including the location of those trials
    - Cultural competence and humility
    - Implicit bias
- In addition to workforce training, it is also important to ensure the diversity among the clinical trial team (e.g., investigators, nurses, research coordinators), especially those who interact with patients on a regular basis.[226]
- Efforts to increase the diversity of the research work force, with specific attention to the inclusion of minority investigators, should be prioritized.

A workforce that is able to relate, empathize, and communicate with patients is better able to build trust and to connect with and provide care for potential study participants. In the context of clinical research, "workforce" pertains to clinicians, investigators, research team members, referring physicians, sponsors, CROs and patient recruitment vendors who are directly or indirectly involved with the research study. A clinical research workforce that is diverse itself is better able to prioritize, connect, care for, and successfully recruit a diverse participant

[226] Davis AM, Hull SC, Grady C, Wilfond BS, Henderson GE. The invisible hand in clinical research: the study coordinator's critical role in human subjects protection. The Journal of Law, Medicine & Ethics. 2002 Sep;30(3):411-9.

Figure 18: Elements of workforce development

- Building capacity among physician and care providers
- Training the current research workforce
  - Implicit bias association
  - Cultural competence and humility
  - Increased understanding of cultures and communities relevant to area(s) of research
- Preparing the workforce of the future
  - Unbiased and open searches for positions
  - Mentoring, sponsoring, and promoting individuals of diverse backgrounds
  - Expanding opportunities for underrepresented minorities

population in research,[227,228,229] and collectively we should strive to diversify the workforce. At the same time, we must train the current workforce in cultural competence and humility and to understand how to approach, welcome, communicate with, and take care of increasingly diverse participant populations. Medical, dental, nursing, and allied healthcare student curricula should be modified so that graduates understand the importance of diversity and inclusion in general and in clinical research specifically. Further, clinicians and referring care providers who are aware of existing clinical research, are knowledgeable of its purpose, and are able to access and navigate its protocols are in a better position to recommend or refer participants to a relevant research study or trial. Figure 18 summarizes some of the elements of workforce development.

Institutions and organizations that promote diversity within the workplace, utilize third party vendors that have a diverse work force, and promote diverse inclusion in clinical trials appear to better support sites and to accommodate necessary modifications for inclusivity of diverse or underrepresented populations in research.[230] Further, organizations that provide cultural competence and humility training (e.g., language classes, ethics training, implicit bias training, diversity of views on illness and treatment) internally to employees and externally to clinical sites, in addition to providing other supportive mechanisms such as translators or study

[227] Alsan M, Garrick O, Graziani G. Does diversity matter for health? Experimental evidence from Oakland. American Economic Review. 2019 Dec;109(12):4071-111.
[228] Boyington JE, Maihle NJ, Rice TK, et al. A Perspective on Promoting Diversity in the Biomedical Research Workforce: The National Heart, Lung, and Blood Institute's PRIDE Program. *Ethn Dis*. 2016; 26(3):379–386.
[229] NIH Scientific Workforce Diversity Toolkit. Available at: https://diversity.nih.gov/toolkit [Accessed 22 June 2020].
[230] Kurt A, Semler L, Meyers M, Porter BG, Jacoby JL, Stello B. Research Professionals' Perspectives, Barriers, and Recommendations Regarding Minority Participation in Clinical Trials. J. Racial and Ethnic Health Disparities. 2017; 4:1166-1174.

information materials developed specifically for linguistically and/or culturally diverse audiences (e.g., translated participant instructions, diaries, informative pamphlets, brochures or booklets) are generally more successful at recruiting racial, ethnic, and otherwise diverse study populations.[231]

A comprehensive workforce development program should have, at a minimum, five components: (1) a commitment from senior leadership to enroll underrepresented and underserved populations to the extent possible (see Chapter 17, "Stakeholder Roles, Responsibilities and Accountability in Promoting Diversity"), (2) training for research professionals and staff, as well as individuals responsible for developing study-related materials, (3) a commitment to recruiting and training a diverse clinical research workforce, (4) ensuring that staff are able to understand and respect cultural considerations of potential populations, and (5) a commitment to health literacy. The success of any given workforce development program, however, is evident only through measuring improvement over time, which could be indicated by a shift in research study enrollment numbers, a value change in implicit association bias results, and/or through a statement of commitment from the executive level at an organization[232] (see "Introduction to Logic Models," "Logic Model: Workforce Development," "Workforce Development Key Performance Indicators (KPIs)" in *Toolkit* and Section 17.1.2 "Public statements of commitment to diversity in clinial research"). This section provides an overview of these components and offers recommendations to increase the diversity and cultural competency of a given workforce.

[231] Clark LT, Watkins L, Piña IL, Elmer M, Akinboboye O, Gorham M, Jamerson B, McCullough C, Pierre C, Polis AB, Puckrein G, Regnante J. Increasing diversity in clinical trials: overcoming critical barriers. Current problems in cardiology. 2019 May 1;44(5):148-72. DOIF: 10.1016/j.cpcardiol.2018.11.002. Epub 2018 Nov 9

[232] Ahmed HR, Strauss DH, Bierer BE. Committing to the Inclusion of Diverse Populations in Clinical Research. Therapeutic Innovation & Regulatory Science. January 2020. DOI 10.1007/s43441-019-00020-6.

10.1 Cultural considerations

Culture refers to systems of knowledge, concepts, values, norms, and practices that are learned and transmitted across generations. This process of meaning-making and social practice does not stem from any single dimension of religion, race, ethnicity, language, socio-economy, ancestry, ability, age, immigration status, or other aspect of background and social experience. Cultures are open, dynamic systems that undergo continuous change over time; in the contemporary world, most individuals and groups are exposed to multiple cultures, which they use to fashion their own identities and make sense of experience.

Figure 19: Inclusion of individuals of the Islamic faith in clinical research

The Islamic faith is practiced by nearly 25% of the global population and is the fastest-growing religion in the world. Islam encourages its followers to adhere to basic principles and texts. An individual's practice of or dedication to any religion can create some barriers to participation in clinical research, and Islam is no exception. For example, understanding places and times of prayer is useful for recruitment and retention of Muslim participants who adhere to these practices, as it can facilitate better scheduling of follow-up visits outside of prayer hours. Additionally, the month of Ramadan, a designated time for introspection and prayer, requires Muslims to abstain from food and liquids during daylight hours (sunrise to sunset). For a Muslim individual interested in joining a study, understanding the requirements for participation (e.g., required study visits or data collection points) and the flexibility of the study protocol are important considerations when deciding to enroll. The investigator's awareness of the religion and willingness to engage in a conversation about accommodating religious needs demonstrates understanding and respect of the potential participant.

To build trust and rapport, and to address challenges faced by a diverse participant population adequately, researchers should understand the background and cultures included in the study population. Awareness of

and "connecting"[233] with a study population requires learning about diverse cultural heritages, norms, and lifestyles that are represented among the study participants (e.g., values, beliefs, language, religious considerations, career styles, family life). Advance exploration and planning are often necessary to develop the preferred or respectful way(s) to communicate with intended population. For instance, a Muslim individual who is interested in joining a study may need time to discuss participation with their family as the decision to participate may not be a individual decision but a family one (see Figure 19). While participants may feel more comfortable working with a researcher who shares some aspects of their background, social groups like racial/ethnic minorities are culturally diverse. Simple racial or ethnic matching of investigators and participants may help improve engagement but by itself does not necessarily address key values and concerns prevalent in the study population.[234]

Investigators, research staff, and sponsors should strive for humility, self-reflection, and "reflexivity" to better understand the cultural considerations of participants and become more actively involved in the relationship among the participant, community and research study.[235,236] This is an ongoing, iterative process that is more effective if modeled by leaders in all stakeholder groups.

It is important to develop a workforce that creates and sustains a culturally informed and respectful environment; the depth of cultural awareness and competency of those involved in recruiting, communicating, and conducting clinical research influences the interactions and communications with potential and enrolled participants. The historical and social influence of research differs across and within cultures and for the individual; potential participants may

[233] Fryer CS, Passmore SR, Maietta RC, Petruzzelli J, Casper E, Brown NA, Butler III J, Garza MA, Thomas SB, Quinn SC. The symbolic value and limitations of racial concordance in minority research engagement. Qualitative health research. 2016 May;26(6):830-41.
[234] Otado J, Kwagyan J, Edwards D, Ukaegbu A, Rockcliffe F, Osafo N. Culturally Competent Strategies for Recruitment and Retention of African American Populations into Clinical Trials. Clin Transl Sci. 2015;8(5):460–466. doi:10.1111/cts.12285
[235] Fryer CS, Passmore SR, Maietta RC, Petruzzelli J, Casper E, Brown NA, Butler III J, Garza MA, Thomas SB, Quinn SC. The symbolic value and limitations of racial concordance in minority research engagement. Qualitative health research. 2016 May;26(6):830-41.
[236] Yeager KA and Bauer-Wu S. Cultural humility: essential foundation for clinical researchers. *Applied Nursing Research*. 2013 Nov; 26(4).

have perspectives that affect their willingness to participate in clinical research.[237] For example, mistrust and skepticism by minority and other underrepresented groups are based in part on historical abuses (e.g., the U.S. Public Health Service Syphilis Study at Tuskegee [the Tuskegee Syphilis Study] in which Black men with syphilis were never told of their diagnosis nor treated, despite the later availability of treatment, in order to observe the natural history of the disease; the use of genetic samples from Havasupai Indians not only for diabetes research but also to track migration patterns; and the unauthorized use of genetic material from Henrietta Lacks to create the HeLa cell line for cancer therapy).[238,239] Further, even after agreeing to participate and enrolling in a research study, some participants may not feel comfortable in an academic medical setting, leading to loss of follow-up.[240] Addressing these potential hesitations and past experiences is best achieved by staff who understand (or may be a part of that group, which is also a way to diversify the staff) and are receptive to discussion, communication, and adapting, when possible, language and expectations. Engagement with the intended participant population prior to trial initiation is central in helping develop study outreach materials, prepare study staff, and foster a presence in and partnerships with the local community (see Chapter 8 "Participant and Community Engagement").[241]

10.2 Training of clinicians and the importance of study teams

As an important referral conduit, clinicians are able to connect potential participants and investigators. Empirical data demonstrate that patients and the public generally look to their

[237] Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggly S. Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. Cancer Control. 2016 Oct;23(4):327-37.
[238] 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. American journal of public health. 2014 Feb;104(2):e16-31.
[239] Pacheco CM, Daley SM, Brown T, Filippi M, Greiner KA, Daley CM. Moving forward: breaking the cycle of mistrust between American Indians and researchers. American journal of public health. 2013 Dec;103(12):2152-9.
[240] Hughson JA, Woodward-Kron R, Parker A, Hajek J, Bresin A, Knoch U, Phan T, Story D. A review of approaches to improve participation of culturally and linguistically diverse populations in clinical trials. Trials. 2016 Dec 1;17(1):263.
[241] Metzger DA. Is Patient Centricity Truly at the core of Clinical Trials? KNect 365 Life Sciences. White Paper. https://knect365.com/clinical-trials-innovation/article/8d4ad6db-0dde-4ddf-8def-5b569c1f4c91/whitepaper-is-patient-centricity-truly-at-the-core-of-clinical-trials [Accessed 22 June 2020]

healthcare providers for health information, advice, and guidance.[242,243] In a poll of more than 1,000 Americans conducted by Research!America,[244] over 72% said that they would likely participate in a clinical trial if it were recommended by a clinician, but only 22% reported that a healthcare provider had ever spoken to them about clinical research.[245] Healthcare providers are an important part of the clinical research enterprise: not only can they help raise awareness of clinical research and of specific availability of a clinical trial, they can also be a trusted resource to their patients, can explain the research in the context of the patient's condition, can serve as a critical referral agent, and can engage as an essential collaborator and participant supporter when a trial is over.

Recognizing that many clinical trials are not a good fit for an individual, a patient may choose not to enroll. Nevertheless, the healthcare provider plays an important role in education not only of the patient but of their family and community. Discussions of clinical research can and should be a routine part of clinical care and interactions.

[242] Virk KP, Kermani F. Language & Culture in Global Trials. Applied Clinical Trials. 2011 Jun 1;20(6):72.
[243] Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. JNCI: Journal of the National Cancer Institute. 2019 Feb 19;111(3):245-55.
[244] Research America. Pool: Majority of Americans would participate in clinical trials if recommended by a doctor. https://www.researchamerica.org/sites/default/files/uploads/clinicaltrialsminorities.pdf. [Accessed 22 June 2020].
[245] These numbers are changing with the COVID-19 pandemic. More health care providers are discussing clinical research, and more individuals are willing to participate in clinical trials. In addition, current changes to the conduct of clinical trials (see Section 13.5.2 "Study conduct and retention") such as more remote visits, telemedicine, and direct shipment of the study drug to the patient's home, will make participation less burdensome for the patient.

Figure 20: Informing healthcare providers (HCP) about available research

- Hospital or division newsletter
- Lunch information sessions at HCP clinic
- Sponsor/CRO in-person visits to HCP clinics
- Sponsor/CRO provision of pamphlets to HCP
- Sponsor presentations at conventions, professional meetings, and congresses
- Registration on clinicaltrials.gov and other repositories
- Sponsor initiatives to describe ongoing studies on their website for patients and healthcare staff to access

Healthcare providers vary in their proclivity to refer their patients into clinical trials; clinicians may simply not have the necessary time or available information to recommend and direct a potential participant for consideration to a clinical trial. A number of studies indicate that physicians often lack knowledge and awareness of trials available in their organization or communities;[246,247] one study indicated that 95% of primary care physicians, 84% of specialists, and 50% of oncologists had limited information or knowledge about open, accruing studies.[248] For healthcare providers to transfer knowledge and awareness to patients, they – and others (e.g., disease-specific patient advocacy groups) – need information and education about the availability of ongoing clinical trials that are currently open to enrollment. Successful ways to achieve this include providing information to health care providers (Figure 20). Healthcare providers reported that the higher their research knowledge and their mental and physical closeness to a trial (e.g., how well they understand the trial, proximity of the research center) the more likely they will be to refer patients into clinical research.[249] Certain resources, such as clinical trial registries (e.g., www.Clinicaltrials.gov, EudraCT, WHO ICTRP), sponsor websites created for patients and healthcare providers to search for applicable trials, disease-specific patient

[246] 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. American journal of public health. 2014 Feb;104(2):e16-31
[247] Schmotzer GL. Barriers and facilitators to participation of minorities in clinical trials. Ethnicity & disease. 2012 Apr 1;22(2):226-30.
[248] Hudson SV, Momperousse D, Leventhal H. Physician perspectives on cancer clinical trials and barriers to minority recruitment. Cancer Control. 2005;12 Suppl 2:93–96.
[249] Getz KA. Enabling healthcare providers as facilitators of patient engagement. Applied Clinical Trials. 2017 Oct; 26(10).

advocacy group communications about trials, are helpful in democratizing information about trial availability.

For complex protocols, busy clinicians may not have time or familiarity to explain the study; this is when the study team or research staff become critical to relieve clinician burden and enhance participant recruitment.[250] A clinical research team that is able to describe the purpose of the research study and the research procedures, and answer participants' questions, can help lessen the dependency on either the provider or the investigator. Well-trained study coordinators, patient navigators, and other research staff are recommended. Training the clinical research team on the skills necessary to support, understand, and communicate with a diverse participant population should be intentional and comprehensive.

Figure 21: Essential elements for a comprehensive diversity training

- Clinical research training
- Privacy and confidentiality training
- Trust and relationship building
- Implicit bias training
- Mindfulness tools for cultural humility

[250] Morain SR, Largent EA. Recruitment and Trial-Finding Apps—Time for Rules of the Road. JNCI: Journal of the National Cancer Institute. 2019 May 11.

Figure 21 provides essential elements of comprehensive training diversity training and Figure 22 provides an example of a success story.[251]

Figure 22: Addressing implicit bias through training

> Vanderbilt University Medical Center's Department of Equity, Diversity partnered with Monroe Carell Jr. Children's Hospital to develop a multifaceted unconscious bias program after hospital data indicated fewer treatments and worse outcomes from patients of Latinx, Black, Native American and other underserved populations. The program involves a three-step process to enhance faculty and employees awareness, education, and mindfulness in everyday interactions. The program highlights the importance of close interpersonal relationships to address unconscious biases and created "*affinity groups*" that bring people together from different races, genders, religions and backgrounds. To date, 25% of employees, faculty and trainees at the Medical Center have been trained in the program and the results are impressive: for example, national representation of underrepresented groups appearing as chairs of all medical schools is 7% - whereas at Vanderbilt it is 17%.

Some data indicate that privacy is a concern of participants, including minorities and underrepresented populations;[252,253,254] appropriate training, therefore, on privacy and participant confidentiality is not only foundational to conducting ethical clinical research but also to addressing participant concerns. Awareness of implicit bias—and training to reduce this bias—are important as well: research staff and health care providers may not discuss a clinical trial with a patient if they believe the individual will not understand the research study, not be interested (and even possibly offended by the suggestion of a research study), not be eligible

[251] Vanderbilt Discover. Addressing Unconscious Bias in Medicine [Internet]. Vanderbilt University Medical Center. April 8, 2020. Available online: https://discover.vumc.org/2020/04/addressing-unconscious-bias-in-medicine/ [Accessed 22 June 2020].
[252] Otado J, Kwagyan J, Edwards D, Ukaegbu A, Rockcliffe BA, Osafo N. Culturally Competent Strategies for Recruitment and Retention of African American Populations into Clinical Trials. Clinical Translational Science. 2015; Volume 8: 460–466
[253] 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. American journal of public health. 2014 Feb;104(2):e16-31
[254] Schmotzer GL. Barriers and facilitators to participation of minorities in clinical trials. Ethnicity & disease. 2012 Apr 1;22(2):226-30.

for the study based on medical characteristics (e.g., minority status, age, disease stage), or not be a reliable study participant (see Section 13.3.1.3 "Investigator discretion").

Sometimes suggesting or requiring implicit bias training is necessary may be difficult for a supervisor or be interpreted adversely (e.g., as implying an attitude that needs correction or a discriminatory action. It may be in the best interest of sponsors, CROs, and institutions, therefore, to require workforce development training for all Institutional Review Board/Research Ethics Committee (IRB/REC) members, investigators and study staff prior to study implementation, or annually as an institutional expectation. Assessing skills and knowledge gained and retained by study staff can be executed by requiring pre-test and post-test evaluations, by using the "see one, do one, teach one" training method,[255] through observation and or improvement in recruitment and retention of underrepresented participants, and/or by routine (not "patient complaint") feedback from participants. Finally, language and clarity of communication are barriers that can be addressed with training (see Section 10.4 "Health literacy and clear communication to support diversity").[256,257,258]

[255] The "see one, do one, teach one" training method is often used in medical training, particularly for practioners in surgery. The phrase reflects the method of teaching whereby a trainee will observe a procedure, perform one on their own, and then teach another trainee how to conduct the procedure.
[256] Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggly S. Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. Cancer Control. 2016 Oct;23(4):327-37.
[257] Wendler D, Kington R, Madans J, Van Wye G, Christ-Schmidt H, Pratt LA, Brawley OW, Gross CP, Emanuel E: Are racial and ethnic minorities less willing to participate in health research? Plos Med 2006, 3(2):e19.
[258] Rivers D, August EM, Sehovic I, Green BL, Quinn GP. A systematic review of the factors influencing African Americans' participation in cancer clinical trials. Contemporary clinical trials. 2013 Jul 1;35(2):13-32.

Figure 23: The Latin American Cancer Research Coalition (LACRC) and the TRUST model

Hispanic/Latinx are the largest and one of the fastest growing subpopulations in the United States. In Washington, DC the Latinx population grew by 28% between 2000 and 2010. Noting the increased need for cancer control and the growing population of Latinxs in DC, the Latin American Cancer Research Coalition (LACRC) was created as an academic coalition, with funding from the National Cancer Institute (NCI) to address the lack of culturally appropriate recruitment and retention strategies for clinical cancer trials. The coalition developed a participatory community model, termed TRUST, based on the inclusion of culturally appropriate infrastructure and recruitment strategies. Included in the model are: employment and upskilling of multicultural and bilingual research staff; access to Latinx media and social networks; hiring of Latinx spokespeople to facilitate community engagement; and use of culturally tailored messages. The success rate for recruitment (defined by the proportion of participants in the research study relative to the number approached) reached an average of 96% for studies that utilized the TRUST models.

Providing trainings on cultural competence and humility and implicit association bias early in both clinical care and research will help to reduce selection bias and improve inclusion.[259,260] Efforts suggest that a knowledgeable, well-trained, interdisciplinary team of researchers, staff, translators, and others can tailor research materials for literacy and linguistic and cultural appropriateness to facilitate recruitment and retention of an underrepresented and culturally diverse participant pool[261] (see Figure 23: "Latin American Cancer Research Coalition (LACRC) and the TRUST Model").

Lastly, with regard to training a workforce on diverse representation in clinical research, positive working relationships among investigators, sponsors, CROs and research teams should be cultivated, as

[259] Dehon E, Weiss N, Jones J, Faulconer W, Hinton E, Sterling S. A systematic review of the impact of physician implicit racial bias on clinical decision making. Academic Emergency Medicine. 2017 Aug;24(8):895-904.
[260] FitzGerald C, Hurst S. Implicit bias in healthcare professionals: a systematic review. *BMC Med Ethics*. 2017;18(1):19. Published 2017 Mar 1.
[261] Sheppard VB, Cox LS, Kanamori MJ, Cañar J, Rodríguez Y, Goodman M, Pomeroy J, Mandelblatt J, Huerta EE, Latin American Cancer Research Coalition (LACRC. Brief report: if you build it, they will come. Journal of general internal medicine. 2005 May 1;20(5):444-7.

these are the individuals who interact and build trust with potential participants.[262] Showing support for staff through comprehensive training, gestures of appreciation, and/or opportunities to learn also helps reduce study staff turnover and fosters better communication with participants that are essential components to establishing trust.[263,264] For example, providing clinical research staff with opportunities to discuss and provide trial feedback, for co-authorship and/or strategic decision-making (e.g., future study selection) are effective ways of promoting job satisfaction.[265]

10.3 Recruiting and training a diverse clinical research workforce

The medical profession is historically not diverse[266, 267,268] and investigators from diverse racial and ethnic groups are underrepresented in clinical research.[269] Changing the trajectory of representation in the health professions and in clinical research is possible with sustained commitments from educational institutions and the professions from an early stage.

The profound importance of improving mentorship and training of young investigators, particularly those of diverse backgrounds (e.g., language, race and ethnicity, sex and gender, socio-economic background) in clinical research is a responsibility of all stakeholders (see

[262] Resources to address cultural competence, the ability of providers and organizations to effectively deliver health care services that meet the social, cultural and linguistic needs of patients, are available. HHS. Office of Population Affairs. Cultural Competence. https://www.hhs.gov/ash/oah/resources-and-training/tpp-and-paf-resources/cultural-competence/index.html [Accessed 22 June 2020]
[263] Mody L, Miller DK, McGloin JM, Freeman M, Marcantonio ER, Magaziner J, Studenski S. Recruitment and Retention of Older Adults in Aging Research: (See editorial comments by Dr. Stephanie Studenski, pp 2351–2352). Journal of the American Geriatrics Society. 2008 Dec;56(12):2340-8.
[264] Manson SM, Jiang L, Zhang L, Beals J, Acton KJ, Roubideaux Y, SDPI Healthy Heart Demonstration Project. Special diabetes program for Indians: retention in cardiovascular risk reduction. The Gerontologist. 2011 Jun 1;51(suppl_1):S21-32.
[265] Baer AR, Zon R, and Lyss AP.The clinical research team. *Journal of Oncology Practice*. 2011; 7(3):188-192.
[266] Watson W. Against the odds: Blacks in the profession of medicine in the United States. Routledge; 2017 Dec 2.
[267] Davis G, Allison R. White coats, black specialists? Racial divides in the medical profession. Sociological Spectrum. 2013 Nov 1;33(6):510-33.
[268] Grumbach K, Mendoza R. Disparities in human resources: addressing the lack of diversity in the health professions. Health Affairs. 2008 Mar;27(2):413-22
[269] Boyington JE, Maihle NJ, Rice TK, et al. A Perspective on Promoting Diversity in the Biomedical Research Workforce: The National Heart, Lung, and Blood Institute's PRIDE Program. *Ethn Dis*. 2016;26(3):379–386. Published 2016 Jul 21. doi:10.18865/ed.26.3.379

Chapter 17 "Stakeholder Roles, Responsibilities and Accountability in Promoting Diversity"). Efforts to employ staff who speak the native language of the majority of patients improves communication, engagement, and trust – critical components that lead to successful clinical research.[270,271] Moreover, employment of research staff who share demographic and cultural characteristics with the study population (e.g., sex, gender, race, ethnicity, age, sexual orientation, cultural background, language) or those with extensive experience with the study population may add acceptability and relevance to the research and to the community.[272] In fact, "racial/ethnic matching," whereby the race or ethnicity of the patient and the researcher are aligned, has been shown to improve participation and is used as a recruitment and retention strategy in clinical research.[273,274,275] The NIH has created the NIH Scientific Workforce Diversity Toolkit,[276] an evidence-based tool to address workforce diversity and inclusion, focusing not only on hiring a diverse workforce but also supporting individuals who are currently in the workforce. The NIH Toolkit includes a recruitment tool that institutions can use to expand their candidate pool to include more diverse talent, address bias in the search process, and provide guidance on and methods for outreach, networking, and mentoring relationships.

[270] Hughson JA, Woodward-Kron R, Parker A, Hajek J, Bresin A, Knoch U, Phan T, Story D. A review of approaches to improve participation of culturally and linguistically diverse populations in clinical trials. Trials. 2016 Dec 1;17(1):263.
[271] Schmotzer GL. Barriers and facilitators to participation of minorities in clinical trials. Ethnicity & disease. 2012 Apr 1;22(2):226-30.
[272] Otado J, Kwagyan J, Edwards D, Ukaegbu A, Rockcliffe F, Osafo N. Culturally Competent Strategies for Recruitment and Retention of African American Populations into Clinical Trials. Clin Transl Sci. 2015;8(5):460–466. doi:10.1111/cts.12285
[273] Burlew AK, Weekes JC, Montgomery LT, Feaster DJ, Robbins MS, Rosa CL, Ruglass LM, Venner KL, Wu LT. Conducting research with racial/ethnic minorities: Methodological lessons from the NIDA Clinical Trials Network. The American journal of drug and alcohol abuse. 2011 Sep 1;37(5):324-32.
[274] Alsan M, Garrick O, Graziani G. Does diversity matter for health? Experimental evidence from Oakland. American Economic Review. 2019 Dec;109(12):4071-111.
[275] Fryer CS, Passmore SR, Maietta RC, Petruzzelli J, Casper E, Brown NA, Butler III J, Garza MA, Thomas SB, Quinn SC. The symbolic value and limitations of racial concordance in minority research engagement. Qualitative health research. 2016 May;26(6):830-41.
[276] NIH Scientific Workforce Diversity Toolkit. 2011 . Available at: https://diversity.nih.gov/sites/coswd/files/images/SWD_Toolkit_Interactive-updated_508.pdf. [Accessed 22 June 2020]

Figure 24: American Society of Clinical Oncology (ASCO)

In 2017, the American Society of Clinical Oncology (ASCO) developed a strategic plan to establish short-term goals to create and enhance programs and opportunities to achieve an oncology workforce that reflects the demographics of the U.S. population it serves. One of its major priorities was to improve and expand mentoring opportunities for early medical school trainees.

A variety of strategies are used to support the broadening inclusivity of the clinical research workforce. In the Programs to Increase Diversity Among Individuals Engaged in Health-Related Research (PRIDE), the NIH's National Heart, Lung, and Blood Institute (NHLBI) supports an all-expense paid summer experience for junior investigators and senior post-doctoral scientists that provides opportunities to explore careers in clinical research.[277] The goal of PRIDE is to increase diversity in the biomedical research workforce and expand the ethnic and racial representation of individuals who pursue research as a career. The 2017 Strategic Plan of the American Society for Clinical Oncology called for increasing racial and ethnic diversity in the oncology workforce[278] (see Figure 24). Eli Lilly and Company, in partnership with the Center for Drug Development and Clinical Trials at Roswell Park Cancer Institute, hosts workshops to train ethnic and racial minority physicians to become clinical trial investigators, ultimately to increase the diversity of clinical trial workforce.[279]

Lastly, the number of multiregional trials conducted in different regions, countries, and continents provides an opportunity to increase the international workforce, which is often a diverse workforce relative to U.S. characterists, and to increase the diversity of the participants enrolled. Sponsors of international trials should provide training wherever trials are sited (see

[277] Boyington JE, Maihle NJ, Rice TK, et al. A Perspective on Promoting Diversity in the Biomedical Research Workforce: The National Heart, Lung, and Blood Institute's PRIDE Program. *Ethn Dis*. 2016;26(3):379–386. Published 2016 Jul 21. doi:10.18865/ed.26.3.379

[278] Diversity in Oncology Initiative. (2016). Retrieved 4 February 2020, from https://www.asco.org/practice-policy/cancer-care-initiatives/diversity-oncology-initiative Winkfield KM, Flowers CR, Mitchell EP. Making the case for improving oncology workforce diversity. American Society of Clinical Oncology Educational Book. 2017 May;37:18-22.

[279] Training Minority Clinical Trial Investigators. (2014). Retrieved 5 February 2020, from https://www.lilly.com/training-minority-clinical-trial-investigators

Section 13.4 "Feasibility assessments and site selection"); communicate expectations of ethical research, participant respect and autonomy; and insist on good clinical practices; and data quality.[280]

10.4 Health literacy and clear communication to support diversity

Health literacy should always be considered in the context of clinical research. Traditionally defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions,[281] health literacy has been reimagined as a bi-directional relationship.

Figure 25: Health literacy best practices

- Use of plain language
- Images relating to specific population
- Multi-format explanations of numeric information
- Application of clear design principles
- Translations and additional cultural considerations that contribute to the creation of materials that are designed specifically for a heterogeneous population.

For more information and examples, see the MRCT Center's Health Literacy in Clinical Research website at https://mrctcenter.org/health-literacy/

The onus and burden should not be placed on the individual and his/her ability to comprehend complex information; rather, the communicator is responsible for developing and sharing health information in ways that are understood. These expectations require that clinical research stakeholders who create participant-facing materials are educated about health literacy issues and are provided with strategies to integrate health literacy best practices into their roles (for examples, see Figure 25). In the context of this document, attention to health literacy supports intersectional solutions that diversity efforts seek to address. Namely, the process of including a representatively diverse population in research is predicated on clear research communications.

[280] Virk KP, Kermani F. Language & Culture in Global Trials. Applied Clinical Trials. 2011 Jun 1;20(6):72.
[281] U.S. Department of Health and Human Services. 2000. *Healthy People 2010*. Washington, DC: U.S. Government Printing Office. Originally developed for Ratzan SC, Parker RM. 2000. Introduction. In *National Library of Medicine Current Bibliographies in Medicine: Health Literacy*. Selden CR, Zorn M, Ratzan SC, Parker RM, Editors. NLM Pub. No. CBM 2000-1. Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services.

One-third of the U.S. population has health literacy levels that are basic or below basic.[282] This statistic is not unique to the United States: limited health literacy impacts access to appropriate health-related services around the world. The European Health Literacy Survey, for example, found that 12% of all respondents have inadequate general health literacy and 35% have problematic health literacy.[283] A survey in Brazil founded that 31.7% of people had limited functional health literacy;[284] a cross-sectional survey of adults conducted in Isfahan, Iran, demonstrated that 79.6% of adults had inadequate health literacy; and a national survey of adults in Taiwan found that 30% had low levels of health literacy.[285] Low health literacy is likely to worsen in the clinical research context, given the complexity of clinical research information and the types of environments in which research conversations typically occur.[286]

Clear communication is especially important for the successful engagement and inclusion of diverse populations. A number of factors may influence an individual's health literacy, including living in poverty, education, race and ethnicity, age, and disability, and the fact that, in the U.S., some of the greatest disparities in health literacy occur among different racial and ethnic minority groups and those who do not speak English as a first language.[287] There have been global efforts to culturally adapt and communicate clinical research materials using relevant verbiage and phraseology with the assistance of local translators who review, translate, and back translate the information contained in the clinical research documents.[288] For example, the "speaking book," a sound recording with pictures that explains to potential participants

[282] Cutilli CC, Bennett IM. Understanding the health literacy of America results of the national assessment of adult literacy. Orthopaedic nursing/National Association of Orthopaedic Nurses. 2009;28(1):27.
[283] Kickbusch I, Pelikan JM, Apfel F, Tsouros AD. Health literacy: The solid facts. 2013. World Health Organization, Regional Office for Europe,[http://www. euro. who. int/__data/assets/pdf_file/0008/190655/e96854. pdf]. 2017.
[284] Apolinario D, Mansur LL, Carthery-Goulart MT, Brucki SM, Nitrini R. Detecting limited health literacy in Brazil: development of a multidimensional screening tool. Health promotion international. 2014 Mar 1;29(1):5-14
[285] Malik M, Zehra Zaidi R, Hussain A. Health literacy as a global public health concern: A systematic review. Journal of Pharmacology & Clinical Research. 2017;4(2):1-7.
[286] As discussed in Section 13.2 "Study question and design," with electronic informed consent, comprehension is improving as potential participant can "click" on any word for a definition. In addition, investigators can follow up with participants to answer questions.
[287] Health Literacy | Healthy People 2020. (2019). Healthypeople.gov. Retrieved 25 November 2019, from https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-health/interventions-resources/health-literacy
[288] Virk KP, Kermani F. Language & Culture in Global Trials. Applied Clinical Trials. 2011 Jun 1;20(6):72.

their rights and roles in the clinical research, was launched by the World Medical Association in 2008.[289]

On a more practical level, thoughtful materials and conversations that seek to address the concerns and questions of individuals who may not be familiar with research and who may need support when considering clinical research participation are important. For instance, simplification of the informed consent document, limiting the "legal language," and using imagery and design principles promote understanding. Research has found that even people with higher health literacy levels prefer simple, plain-language messaging.[290] Implementing health literacy best practices should be a priority when striving for inclusive representation of diverse populations in research.

An appreciation for the importance of "person-first" (or "people-first") language is emerging. People with a disability or disease are not defined by that disease or disabiltiy: terms such as the "handicapped" should be replaced with "people with disabilities;" "diabetics" or "epileptics" should be replaced by "individuals with diabetes," "persons with epilepsy." This is similar to the evolution of the term "research subject." Traditionally, research participants were termed "subjects" until it was appreciated—by asking participants—that the preferred word choice was "participant." If it is unclear how to refer to someone with a disease, condition, or disability, it is best to ask them. Documents should be edited for person-first language choice, demonstrating understanding, dignity and respect.

[289] WMA - The World Medical Association-Speaking Books. (2020). Retrieved from https://www.wma.net/publications/speaking_books/ [Accessed 22 June 2020]
[290] Andrus MR, Roth MT. Health literacy: a review. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2002 Mar;22(3):282-302.

10.5 Recommendations

RECOMMENDATIONS
For Sponsors, Investigators, Providers, Clinical Research Sites and Healthcare Institutions:

- Develop a comprehensive workforce training and development program as part of the organization's strategic plan to recruit, train, and mentor a diverse workforce to achieve better intercultural responsiveness.
- Create and expand mentoring opportunities, including satellite or sister offices and connection networks, that are available for new investigators and study teams from underrepresented groups.
- Intentionally guide the clinical research team on the skills necessary to support, understand, and communicate with a diverse participant population through a comprehensive training plan that includes trust /relationship building, and training in implicit bias detection and reduction and in cultural competence and humility.
- Improve and encourage the career development and leadership opportunities available for people with diverse backgrounds.
- Establish a workforce that is able to adopt and implement health literacy best practices in clinical research to ensure an inclusive environment.

Part D – Data Standards and Analysis

This guidance is focused on the importance of diverse inclusion in clinical research. To inform the general population, subpopulations, and individuals regarding the risk and benefit of any clinical trial, each protocol must define, in advance, the data that will be collected and the procedures that will be necessary to collect that data. Therefore, what data to collect, and how to collect them, must be considered as a part of study design and in advance of study initiation. We therefore discuss data variables, data collection, and data standards now, before study design and study conduct, and restrict the discussion to issues relevant to inclusion of diverse populations. And because data collection informs data analysis, we discuss issues (again relevant to inclusion and diversity) of data analysis directly thereafter.

The overall strategy for data collection, reporting, and analysis will be protocol-specific and will depend on the disease or condition being studied. Developing the demographic data collection plan, for instance, for a study involving treatment of depression of transgender youth will be very different than one of novel treatments of a rare subtype of cancer, and different again from a protocol relating to treatment of type 2 diabetes. For any protocol, the specific data necessary to inform the planned analysis must be determined, not only to inform the planned analysis but also to comply with subsequent submission requirements to regulatory authorities, other agencies, funders, and sponsors, as required. In addition, as requirements for open data access evolve, good data stewardship including standards are essential for secondary research.

The primary data should be collected in the most granular form possible such that the data can then be categorized, shared, and/or aggregated in different ways for different purposes. Only after identifying the specific granular data that will be collected can the risks of that collection, specific to the subgroup and population, be considered, mitigated, and explained to potential participants.

11. Data Variables and Collection

11.1 Background

The collection of demographic and non-demographic data variables, ideally in a standardized format, is critical to enable not only valid statistical analyses but also to enable data aggregation and interoperability over time and across different trials. Currently, the lack of uniformity in the collection and reporting of common demographic and non-demographic variables, including age, race, ethnicity, sex, gender, and social determinants of health, both within and across different therapeutic areas in clinical research, limits utility and progress in understanding.[291,292,293,294,295] Challenging data collection and analyses is a lack of clarity and/or consistency in definition: demographic and non-demographic variables are often defined, named, collected, and reported differently, making it difficult to compare or combine trial results. This lack of standardization limits the assessment of heterogeneity of treatment effect across different subgroups (see Chapter 12 "Approach to Data Analysis"). Assessment of diverse representation and inclusion in clinical research can better be achieved if these variables are defined uniformly and collected consistently and routinely at the most granular level.

[291] Shanawani H, Dame L, Schwartz DA, Cook-Deegan R. Non-reporting and inconsistent reporting of race and ethnicity in articles that claim associations among genotype, outcome, and race or ethnicity. Journal of medical ethics. 2006 Dec 1;32(12):724-8.
[292] López MM, Bevans M, Wehrlen L, Yang L, Wallen GR. Discrepancies in race and ethnicity documentation: a potential barrier in identifying racial and ethnic disparities. Journal of racial and ethnic health disparities. 2017 Oct 1;4(5):812-8.
[293] Petkovic J, Trawin J, Dewidar O, Yoganathan M, Tugwell P, Welch V. Sex/gender reporting and analysis in Campbell and Cochrane systematic reviews: a cross-sectional methods study. Systematic reviews. 2018 Dec;7(1):113.
[294] Welch V, Doull M, Yoganathan M, Jull J, Boscoe M, Coen SE, Marshall Z, Pardo JP, Pederson A, Petkovic J, Puil L. Reporting of sex and gender in randomized controlled trials in Canada: a cross-sectional methods study. Research integrity and peer review. 2017 Dec;2(1):15.
[295] Rajakannan T., Fain, K., Williams R., Tse,T., Zarin D. Reporting of Sex and Gender in Clinical Trial Protocols and Published Results | Peer Review Congress.Available from: https://peerreviewcongress.org/prc17-0346 [Accessed 22 June 2020].

Consistency in the use of standard, controlled vocabularies and the use of standards in data collection is important.[296] A minority of important demographic variables are discrete, nonoverlapping, and discontinuous: biological sex at birth is one example, although in rare instances, more than two groups (male/female) exist (e.g., intersex individuals whose sex at birth, including genitals, gonads, and hormones, do not fit a binary pattern of assignment). In many or most cases, however, variables exist as a continuum (e.g., age) or are heterogeneous (e.g., race and ethnicity). Distinction is difficult, and even the definition of some variables is unclear or fluid (e.g., Facebook offers over 70 gender options to choose from),[297] or are influenced by social constructs and/or geographic location (e.g., ethnicity, language). With the increased interest in data sharing and transparency, including individual participant-level data and real world data, shared—and machine-readable—data and metadata should be available and harmonized.[298] Harmonized data collection and reporting, especially for core cross-cutting concepts, would allow (1) comparison of results from research, (2) data aggregation and interoperability, (3) analysis of consistent data variables, and (4) evidence generation.

The demographic and non-demographic data variables collected as part of clinical research will depend on the disease or condition being studied. Not all variables need to be collected for all research. Careful consideration of the biological significance or impact relating to genetic and physiological ("intrinsic") versus cultural and environmental ("extrinsic") factors on the safety and efficacy of a therapeutic product should be made during protocol development and design. Appendix A of the ICH Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data,

[296] The development of standardized dictionaries and approaches has already been demonstrated to be helpful in other domains. The Medical Dictionary for Regulatory Activities (MedDRA) is a validated international medical terminology dictionary used by regulatory authorities, industry, and academia from pre-market clinical development (phase 1-3 clinical trials) to post-market activities (phase 4 clinical trials, pharmacovigilance), and for safety information data entry, retrieval, evaluation, and presentation. In addition, MedDRA has been endorsed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as the adverse event classification dictionary. As another example, CDASH establishes a standard method to collect data consistently across studies and sponsors allowing greater transparency, consistency, and potentially interoperability.

[297] Williams, R. (2014). Facebook's 71 gender options come to UK users. Telegraph.co.uk. Retrieved 11 November 2019, from https://www.telegraph.co.uk/technology/facebook/10930654/Facebooks-71-gender-options-come-to-UK-users.html

[298] Kush, R., & Goldman, M. (2014). Fostering responsible data sharing through standards. *New England Journal of Medicine*, *370*(23), 2163-2165. doi: 10.1056/NEJMp1401444

E5(R1), is frequently cited as a framework to recognize the intrinsic and extrinsic variables related to different populations that may impact the effect of a product.[299]

Over the last several decades, substantial efforts have sought to establish standard data collection for clinical trials, most significantly in the consensus-based, standardized collection format developed by the Clinical Data Interchange Standards Consortium (CDISC).[300] CDISC is an international standards development organization that creates data standards with the goal of enabling data interoperability in clinical and translational research.[301] CDISC sets forth controlled terminology for the collection of safety and efficacy data variables. The standards are required for electronic submission to health regulatory authorities in the United States and Japan and are recommended in Europe and China.[302,303] Clinical Data Acquisition Standards Harmonization (CDASH) is the foundational standard created by CDISC to establish a standard way to collect research data consistently across studies and sponsors. The standard data collection formats and structures are free and available for download on the CDISC website,[304] and the supporting terminology for these collection standards are free and available to download on the National Cancer Institute's website.[305] While not all data categories have been standardized, adoption of CDISC standards, where they exist, have enabled interoperability.

The *collection* of data variables should not be confused with the *reporting* of data variables that are frequently grouped in categories in any submission to regulatory authorities, funding agencies, ethics committees, other oversight bodies (e.g., data monitoring committees), or others (e.g., journal editors, registration and reporting registries such as ClinicalTrials.gov,

[299] *Ethnic Factors in the Acceptability of Foreign Clinical Data : ICH*. (2019). *Ich.org*. Retrieved from https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf [Accessed 22 June 2020]
[300] See https://www.cdisc.org [Accessed 22 June 2020]
[301] Hume S, Chow A, Evans J, Malfait F, Chason J, Wold JD, Kubick W, Becnel LB. CDISC SHARE, a Global, Cloud-based Resource of Machine-Readable CDISC Standards for Clinical and Translational Research. AMIA Summits on Translational Science Proceedings. 2018;2018:94.
[302] Hume S, Chow A, Evans J, Malfait F, Chason J, Wold JD, Kubick W, Becnel LB. CDISC SHARE, a Global, Cloud-based Resource of Machine-Readable CDISC Standards for Clinical and Translational Research. AMIA Summits on Translational Science Proceedings. 2018;2018:94.
[303] CDISC Terminology - National Cancer Institute. NCI Enterprise Vocabulary Services. 2017. Available from: https://www.cancer.gov/research/resources/terminology/cdisc. [Accessed 22 June 2020]
[304] See CDASH (2019). Available at: https://www.cdisc.org/standards/foundational/cdash [Accessed 22 June 2020]
[305] CDISC Terminology - National Cancer Institute. NCI Enterprise Vocabulary Services. 2017. Available from: https://www.cancer.gov/research/resources/terminology/cdisc. [Accessed 22 June 2020]

EudraCT, WHO ICTRP). Grouping data into categories is done to achieve more meaningful subgroup analysis – by combining subsets that are thought to respond similarly to the treatment so that a signal of response (or lack of response) may be more easily detected. For example, categorical groupings for age may include selecting median age cutoffs to compare more clinically relevant age subgroups (e.g., pre and post menopausal). Importantly, some data categories have been defined not by biology or objective measures but through a cultural, political, or historical lens that cannot be adopted globally. For example, the FDA and NIH require collection and reporting of ethnic categories that are U.S.-centric (e.g., Hispanic or not Hispanic in the U.S., a designation that loses relevance outside the U.S.).[306]

Outside the U.S., other countries have their country-specific classifications (based on religion, citizenship, legal nationality, language, caste, tribe, etc.), identifying other factors that may covary with health.[307] In Europe, many countries utilize some proxy measures to gather data on racial and ethnic origin, [308] and often depend upon the objective for which the data will be used. In Germany, data on ethnic origin is often designated by migration background, birthplace of parents, language spoken at home, religion or beliefs, and other proxies. In France, geographical origins are indicated by nationality or grouped by geographical area, migration backgrounds are often tracked, and an "immigrant" is defined by the country of birth not the citizenship at birth.[309] And for some important factors such as social determinants of health (see Section 11.5 "Social determinants of health") —factors that may impact health outcomes—data have not been routinely collected nor are there universal standards, definitions, or data collection templates.[310]

---

[306] Centers for Disease Control and Prevention. CDC Wonder: Office of Management and Budget (OMB) Directive No. 15: Race and Ethnic Standards for Federal Statistics and Administrative Reporting. Available at: https://wonder.cdc.gov/wonder/help/populations/bridged-race/directive15.html [Accessed 22 June 2020]

[307] United Nations Statistics Division - Demographic and Social Statistics. (2019). Unstats.un.org. Retrieved 28 October 2019, from https://unstats.un.org/unsd/demographic/sconcerns/popchar/popcharmethods.htm#E [Accessed 22 June 2020]

[308] Farkas, L. Analysis and comparative review of equality data collection practices in the European Union: Data collection in the field of ethnicity. Retrieved from doi:10.2838/447194 http://ec.europa.eu/newsroom/just/document.cfm?action=display&doc_id=45791 [Accessed 22 June 2020]

[309] Farkas, L. Analysis and comparative review of equality data collection practices in the European Union: Data collection in the field of ethnicity. Retrieved from doi:10.2838/447194 http://ec.europa.eu/newsroom/just/document.cfm?action=display&doc_id=45791 [Accessed 22 June 2020]

[310] A future consideration for solving the lack of information on social determinants of health would be to link the clinical trial database with health and other external data. Technological solutions may be helpful in this regard,

The Diversity in Clinical Trials Workgroup set out to identify common approaches to defining and collecting data elements and to provide recommendations, where feasible, of common approaches and strategies for data collection using a standard format. This chapter provides an overview of the challenges and opportunities in data definitions and data collection of age, race and ethnicity, sex and gender, and social determinants of health. In the absence of international standards and in order to facilitate consistent data collection of clinical research demographic and non-demographic data, the MRCT Center Diversity Workgroup has developed a standard data collection tool (see "Data Variables Tool" in *Toolkit*).

Wherein common approaches have not been standardized, we recommend research and a consensus process to advance the field. Any such research and concensus process should involve consultation and/or participation of representatives of the groups in question.

11.2 Age

Age is a universal baseline variable that is routinely collected from clinical research participants.[311] Age is often collected as a continuous variable, and in many cases grouped into categories for further analysis and reporting. Age, whether collected in days, months, or years, acts as a proxy for biological changes that occur throughout a person's life. In clinical research, representation of age at either end of the spectrum (e.g., the elderly and newborns, infants, and children) has historically been low. Underrepresentation persists despite the recognition of the importance of testing therapeutic interventions across all applicable age groups that use or are intended to use the intervention.

Individuals above age 65 are poorly represented in clinical trials.[312,313] An FDA analysis of age-related enrollment in cancer trials supporting registration from 2005-2015 concluded that older

although privacy and confidentiality—and permission to access these data—must be maintained. Even if it were possible to collect the data, common data standards and definitions are necessary.

[311] Date of birth is collected when allowed.

[312] Shenoy P, Harugeri A. Elderly patients' participation in clinical trials. Perspectives in clinical research. 2015 Oct;6(4):184.

[313] Denson AC, Mahipal A. Participation of the elderly population in clinical trials: barriers and solutions. Cancer Control. 2014 Jul;21(3):209-14.

adults (those above age 65) were underrepresented as a subgroup, and those older than 75 were even less well represented.[314] Despite the fact that the majority of people diagnosed with cancer are above age 65 years old, phase 3, randomized, multigroup cancer clinical trials tend to enroll younger trial participants.[315] And that remains true despite the fact that instuments for characterizing physical frailty in patients older than 65 years have been published.[316] In the absence of empirical data, oncologists accommodate adults over the age of 65 by extrapolating treatment plans based on data from younger, healthier cohorts. However, these younger cohorts generally have fewer comorbidities, are on fewer medications (decreasing the possibilities of drug-drug interactions), have higher medication tolerance, and lower risks of adverse drug reactions.[317]

Children are also poorly represented in clinical trials and similar extrapolation is done when prescribing treatment plans instead of doing pediatric specific drug development and research. In many cases, children experience different treatment responses as compared to adults as well as variation of adverse events and morbidity across the pediatric age range .[318] Moreover, the changes from infancy to young adulthood are incompletely understood.[319] Biological, physiological, and psychological changes occur from neonatology through infancy, childhood, and adolescence; categories of age represent proxies for these changes.[320] Importantly, there is

[314] Singh H, Kanapuru B, Smith C, Fashoyin-Aje LA, Myers A, Kim G, Pazdur R. FDA analysis of enrollment of older adults in clinical trials for cancer drug registration: a 10-year experience by the U.S. Food and Drug Administration.
[315] Singh H, Kanapuru B, Smith C, Fashoyin-Aje LA, Myers A, Kim G, Pazdur R. FDA analysis of enrollment of older adults in clinical trials for cancer drug registration: a 10-year experience by the U.S. Food and Drug Administration.
[316] European Medicines Agency. Reflection paper on physical frailty: instruments for baseline characterization of older populations in clinical trials. 9 January 2018. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-physical-frailty-instruments-baseline-characterisation-older-populations-clinical_en.pdf. [Accessed 2 August 2020].
[317] Abbasi J. Older Patients (Still) Left Out of Cancer Clinical Trials. JAMA. 2019 Oct 24.
[318] Williams K, Thomson D, Seto I, Contopoulos-Ioannidis DG, Ioannidis JP, Curtis S, Constantin E, Batmanabane G, Hartling L, Klassen T. Standard 6: age groups for pediatric trials. Pediatrics. 2012 Jun 1;129(Supplement 3):S153-60.
[319] Cole JH, Marioni RE, Harris SE, Deary IJ. Brain age and other bodily 'ages': implications for neuropsychiatry. Molecular psychiatry. 2019 Feb;24(2):266-81.
[320] Interestingly, a gap in research also exists for older adolescents and young adults (ages 15- 39), particularly evident in oncology, wherein the incidence and type of oncologic disorders changes with age. See Freyer DR, Seibel NL. The clinical trials gap for adolescents and young adults with cancer: recent progress and conceptual framework for continued research. Current pediatrics reports. 2015 Jun 1;3(2):137-45.

a lack of consistent and clinically meaningful age group distinctions in clinical research data collection and reporting.[321]

11.2.1 Data standards for collecting age in a clinical trial

Trial design and data collection should account for age and developmental differences throughout aging, and specifically within the pediatric and elderly populations, when appropriate. Whether age is important should be considered during the study design, and if so, other key variables that may reflect underlying biological differences should be collected simultaneously.[322] The protocol itself should justify any upper and/or lower age cutoffs (see Section 13.3 "Eligibility criteria").

In all protocols and/or case report form (CRF) completion guidelines, some standards for data collection of age parameters should be specified, as allowable by local law:

- At the time of collection, age parameters should be recorded as a discrete variable at the individual participant level rather than by age range,[323] consistent with CDISC CDASH data standards.[324]
- Age should be collected at study enrollment (often termed baseline) by date of birth.
    - Note: If there are limitations to collecting date of birth (often related to national- or region-specific privacy laws), the data collection tool should provide a field for "Age", and specify the Age Unit (e.g., years, months).
- Collection of date of birth: The data collection tool should be specific as to the order of terms (MM/DD/YYYY vs. DD/MM/YYYY).

[321] Williams K, Thomson D, Seto I, Contopoulos-Ioannidis DG, Ioannidis JP, Curtis S, Constantin E, Batmanabane G, Hartling L, Klassen T. Standard 6: age groups for pediatric trials. Pediatrics. 2012 Jun 1;129(Supplement 3):S153-60.
[322] Williams K, Thomson D, Seto I, Contopoulos-Ioannidis DG, Ioannidis JP, Curtis S, Constantin E, Batmanabane G, Hartling L, Klassen T. Standard 6: age groups for pediatric trials. Pediatrics. 2012 Jun 1;129(Supplement 3):S153-60.
[323] And as consistent with country regulations and laws.
[324] CDISC CDASH (2017) Clinical Data Acquisition Standards Harmonization: Implementation Guide for Human Clinical Trials Version 2.0. Access via download from CDISC website: https://www.cdisc.org/standards/foundational/cdash/cdashig-v2-0-0 [Accessed 22 June 2020]

- Data definitions, format, and necessary metadata should be defined during trial planning and communicated to the trial investigators and their study teams, and the CROs, as appropriate.
- Metadata should be available and attached to data formats.

11.2.2 Regulatory guidance on reporting age categories in the United States

The U.S. FDA has published a series of guidelines related to the collection and categorization of demographic data in device clinical trials, including age, and these guidelines for devices have since been adopted for reporting of drugs and biologics.[325] The FDA's guidance on a standardized approach is based on the Office of Management and Budget (OMB) Directive 15[326] and developed in accordance with section 4302 of the Affordable Care Act,[327] the U.S. Department of Health and Human Services (HHS) Implementation Guidance on Data Collection Standards for Race, Ethnicity, Sex, Primary Language and Disability Status,[328] and the Food and Drug Administration Safety and Innovation Act (FDASIA) Section 907 Action Plan.[329] The following guidances (Table 6) aim to improve the completeness and quality of subgroup data:

[325] U.S. Food and Drug Administration. Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies: Guidance for Industry and Food and Drug Administration Staff.
[326] (2019). *Whitehouse.gov*. Retrieved 25 September 2019, from https://www.whitehouse.gov/wp-content/uploads/2017/11/Revisions-to-the-Standards-for-the-Classification-of-Federal-Data-on-Race-and-Ethnicity-October30-1997.pdf
[327] Fact Sheet - Improving Data Collection to Reduce Health Disparities. Retrieved from https://minorityhealth.hhs.gov/assets/pdf/checked/1/Fact_Sheet_Section_4302.pdf
[328] *HHS Implementation Guidance on Data Collection Standards for Race, Ethnicity, Sex, Primary Language, and Disability Status*. (2015). *ASPE*. Retrieved 25 September 2019, from https://aspe.hhs.gov/basic-report/hhs-implementation-guidance-data-collection-standards-race-ethnicity-sex-primary-language-and-disability-status
[329] *Inclusion of Demographic Subgroups in Clinical Trials*. (2019). *U.S. Food and Drug Administration*. Retrieved 25 September 2019, from https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fdasia-section-907-inclusion-demographic-subgroups-clinical-trials

Table 6: Guidance on reporting age categories

FDA GUIDANCE	RECOMMENDATION	APPROXIMATE AGE RANGE
Premarket Assessment of Pediatric Medical Devices (2014)[330]	Offers age grouping for the pediatric population. The FDA acknowledges that these divisions are somewhat arbitrary and that additional considerations should be made apart from chronological age including body weight, body size, physiological development, neurological development and neuromuscular coordination.	**Neonates**: birth through first 28 days of life **Infants**: 29 days to less than 2 years **Children**: 2 years to less than 12 years **Adolescent**: Age 12 through 21 (up to but not including 22nd birthday)
E11 (R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population[331]	Complements the original E11 Clinical Investigation of Medicinal Products in the Pediatric Population Guidance published in 2000). The objective of this document is to complement and provide clarification and current regulatory perspectives in pediatric drug development.	**Preterm**[332] **newborn infants** and **Term newborn infants:** 0 to 27 days **Infants and Toddlers**: 28 days to 23 months **Children:** 2 to 11 years

[330] Food and Drug Administration. Premarket Assessment of Pediatric Medical Devices: Guidance for Industry and Food and Drug Administration Staff. Document issued March 24, 2014. Available at: https://www.fda.gov/media/73510/download. p4. Accessed 12 March 2020.
[331] Center for Drug Evaluation and Research. E11(R1) Addendum: Clinical Investigation of Medicinal Products in the [Internet]. U.S. Food and Drug Administration. FDA; [cited 2020Mar17]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11r1-addendum-clinical-investigation-medicinal-products-pediatric-population
[332] Preterm babies are considered newborn from the birth date to expected date of delivery plus 28 days

		Adolescents: 12 to 16-18 years dependent on region
Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies (2017)[333]	Considers grouping participants by age groups as applicable to the therapeutic area. The guidance states that, "*FDA does not define specific age for the geriatric population due to the different considerations for the wide variety of medical devices and diagnostics.*"	As applicable. For geriatric populations, recommends stratifying age as 65-74 years ≥75 years based on relevant disease characteristics, but may be more granular
Additional U.S.-based Initiatives		
ClinicalTrials.gov	Allows the reporting of age as (1) a continuous variable with mean age and standard deviation or (2) a categorical variable in a customizable format appropriate to the investigators' study, or (3) a pre-specified categorization (see next column)	**If prespecified:** **Young**: ≤ 18 years **Adult**: 18-65 years **Older** Adult: ≥ 65 years

[333] Food and Drug Administration. Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies. Document issued September 2017. Available at: https://www.fda.gov/media/98686/download. [Accessed 22 June 2020].

11.2.3 Regulatory guidance on reporting age categories in ex-U.S. regions

The European Medicines Agency (EMA) provides guidance on the specifics of aggregate results sharing in its clinical trials registration portal EudraCT.[334] Table 7 illustrates the categories that are pre-specified for age.

Table 7: Pre-specified age entry categories in EutraCT result sharing

SUBGROUP	APPROXIMATE AGE RANGE
In Utero	
Preterm newborn	Gestational age < 37 weeks
Newborns	0-27 days
Infants & toddlers	28 days – 23 months
Children	2-11 years
Adolescents	12-17 years
Adult	18-64 years
Old Adult	65-84 years
Older Adult	Over 85 years

It is interesting that even between the U.S. and European Union (EU) regulatory agencies, reporting of a non-controversial variable such as age is not harmonized. The age at which one is considered to be an adult can differ across countries. The absence of standard reporting formats, data definitions, and groupings render data integration and analyses difficult and speaks to the importance of collecting age as a continuous variable, in order to summarize and/or report as required by the regulatory authority.

[334] EudraCT: Results related documentation. (at EudraCT result related data dictionary). Available at: https://eudract.ema.europa.eu/result.html. [Accessed 22 June 2020].

11.3 Race and ethnicity

The collection of race and ethnicity data in clinical research is complex,[335,336] in part due to lack of agreement around the definition of terms and categorizations in biomedicine ,[337,338] and in part due to their geographic and cultural significance, rooted in ancestry but often expressed as a lived social experience. While these variables are routinely studied in health disparities and health equity research,[339 340,341] the appropriateness of their application in drug trials as proxies for biological or genetic differences is debated[342,343,344] (and see Chapter 2 "The Case for Diversity in Clinical Research"). Although some regulatory agencies and journals have called for standardization of the terms race and ethnicity, and for valid values of those data elements, for consistent reporting, neither standardization nor consistency have been achieved.[345]

In many countries across the globe, the official enumeration of the population (i.e., the national or international census) utilizes a classification system based on race, ethnicity, and/or national

[335] Caulfield T, Fullerton SM, Ali-Khan SE, Arbour L, Burchard EG, Cooper RS, Hardy BJ, Harry S, Hyde-Lay R, Kahn J, Kittles R. Race and ancestry in biomedical research: exploring the challenges. Genome medicine. 2009 Dec;1(1):8.
[336] Corbie-Smith G, Henderson G, Blumenthal C, Dorrance J, Estroff S. Conceptualizing race in research. Journal of the National Medical Association. 2008 Oct 1;100(10):1235-43.
[337] Brown M, PLoS Medicine Editors. Defining human differences in biomedicine.
[338] Lee C. "Race" and "ethnicity" in biomedical research: how do scientists construct and explain differences in health?. Social Science & Medicine. 2009 Mar 1;68(6):1183-90.
[339] Burchard EG, Ziv E, Coyle N, Gomez SL, Tang H, Karter AJ, Mountain JL, Pérez-Stable EJ, Sheppard D, Risch N. The importance of race and ethnic background in biomedical research and clinical practice. New England Journal of Medicine. 2003 Mar 20;348(12):1170-5.
[340] Genetics Working Group. (2005). The use of racial, ethnic, and ancestral categories in human genetics research. *The American Journal of Human Genetics*, *77*(4), 519-532.
[341] Mersha TB, Abebe T. Self-reported race/ethnicity in the age of genomic research: its potential impact on understanding health disparities. Human genomics. 2015 Dec 1;9(1):1.
[342] Cohn JN. The use of race and ethnicity in medicine: lessons from the African-American Heart Failure Trial. The Journal of Law, Medicine & Ethics. 2006 Sep;34(3):552-4.
[343] Cho MK. Racial and ethnic categories in biomedical research: there is no baby in the bathwater. The Journal of Law, Medicine & Ethics. 2006 Sep;34(3):497-9.
[344] Gutin I. Essential (ist) medicine: promoting social explanations for racial variation in biomedical research. Medical humanities. 2019 Sep 1;45(3):224-34.
[345] Kanakamedala P, Haga SB. Characterization of clinical study populations by race and ethnicity in the biomedical literature. Ethnicity & disease. 2012;22(1):96.

origin.[346] Categorizations vary widely from country to country and are obscured by the ambiguity associated with the meaning of the terms. For example, "race" in one country may be termed "ethnicity" in another; "nationality" may mean "ancestry" in some contexts and "citizenship" in others. These complexities exist within countries as well, where one term can be used interchangeably in different situations.[347,348] For example, in the U.S., the term African-American is commonly used to describe race, and in other circumstances, to specify race and ancestry.

Further, the categorization of people by race is not socially or legally acceptable in many countries, most notably France and Germany, where the collection or use of "race" data are disallowed by law, but other categories of demographic data collection may still be allowed. [349] In Rwanda, ten years after ethnic tensions resulted in genocide, ethnicity designations have been outlawed.[350] Conversely, in South Africa, racial categories that were created in the mid-20th century under the apartheid government continue to be used in studies of genetic predisposition to diseases. Differing conventions in racial and ethnic categorization create difficulty in transnational collaborative research, data aggregation, and comparisons across international studies.[351]

In addition to different terms and different classification systems, the way a researcher elicits race and ethnicity data will impact the result. Race and ethnicity should be self-reported (see

[346] Morning A. (2015) Ethnic Classification in Global Perspective: A Cross-National Survey of the 2000 Census Round. In: Simon P., Piché V., Gagnon A. (eds) Social Statistics and Ethnic Diversity. IMISCOE Research Series. Springer, Cham

[347] Farkas, L. Analysis and comparative review of equality data collection practices in the European Union: Data collection in the field of ethnicity. Retrieved from doi:10.2838/447194 http://ec.europa.eu/newsroom/just/document.cfm?action=display&doc_id=45791 [Accessed 22 June 2020]

[348] Morning A. (2015) Ethnic Classification in Global Perspective: A Cross-National Survey of the 2000 Census Round. In: Simon P., Piché V., Gagnon A. (eds) Social Statistics and Ethnic Diversity. IMISCOE Research Series. Springer, Cham,

[349] Farkas, L. Analysis and comparative review of equality data collection practices in the European Union: Data collection in the field of ethnicity. Retrieved from doi:10.2838/447194 http://ec.europa.eu/newsroom/just/document.cfm?action=display&doc_id=45791 [Accessed 22 June 2020]

[350] Lacey M. A decade after massacres, Rwanda outlaws ethnicity. The New York Times. April 9, 2004. Available at: https://www.nytimes.com/2004/04/09/world/a-decade-after-massacres-rwanda-outlaws-ethnicity.html [Accessed 22 June 2020]

[351] Braun L, Fausto-Sterling A, Fullwiley D, Hammonds EM, Nelson A, Quivers W, Reverby SM, Shields AE. Racial categories in medical practice: how useful are they?. PLoS medicine. 2007 Sep 25;4(9):e271.

("Case Study: Bucindolol" in *Toolkit*), but individuals charged with demographic data collection may assume to know the appropriate entry rather than ask the participant. Questions should be asked in a standard order (e.g., questions about ethnicity precede race) with scripted questions. Individuals assigned to collect personal data should be cognizant of geographic variations and cultural sensitivities, asking questions that are locally respectful and internationally meaningful for the research.

Questions about race and ethnicity differ depending on the country and geographic region. In the U.S., questions are scripted (the first question should collect ethnicity data, "Do you consider yourself Hispanic or Latino or not Hispanic or Latino," followed by a second question on race) in a way that has little or no relevance outside the U.S. Similarly, race classification within the U.S.—including "American Indian or Alaska Native", and "Native Hawaiian or other Pacific Islander"—has no or little relevance outside the U.S. Indeed, in other countries, there are many indigenous populations but no common system for capturing identities. Finally, the researcher may be limited by the available responses in the "box" on the data collection or electronic data capture form that may be available; nevertheless, the researcher must comply whether or not the given race and ethnicity choices reflects the trial participant's self report. And of course, there is racial ambiguity that leads to further challenges. For example, do individuals from Egypt identify as "of African descent," "North African," or "White"? As discussed in Chapter 2 "The Case for Diversity in Clinical Research," designations are important for understanding any degree of biological heterogeneity (albeit a poor surrogate, and other differentiators are likely more relevant) and for social equity reasons. Global cooperation will be required to develop consensus on a system for capturing race, ethnicity, and other data.

11.3.1 Data standards for collecting race and ethnicity in clinical research

Having a standardized method of collecting race, ethnicity, and/or ancestry data enables the results of studies to be directly compared and, if appropriate, data to be interoperable and combined. In addition, standardized methodologies render collaboration easier.

Citing potential ethnic differences, the ICH Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH E5[R1]) acknowledged that national authorities often required local replication of clinical trials to detect any differences in a medicine's safety, efficacy, or dose

regimen. The ICH E5(R1) guidance identifies three major racial groups "most relevant" to the ICH regions: Asian, Black, and Caucasian.[352, 353]

CDISC has developed terminology to describe categories of race and ethnicity.[354] A number of major national authorities including the United States, Japan, Europe, and China recommend or require data to be submitted using CDISC CDASH standards. CDISC CDASH Version 2.0 expanded race and ethnicity categories, based on country of origin, and did it in such a way that the categories roll up to and accommodate the U.S. requirements (see Section 11.3.2 "Regulatory guidance on reporting age categories in the United States"). While the expanded CDASH categories are more comprehensive, they do not always include the ethnic classification systems used by specific countries. It is recommended that additional race and ethnicity values that are not included in current CDISC terminology publications be requested as additions through the CDISC new term request mechanism.[355]

In order to facilitate consistent data collection of clinical research demographic and non-demographic data, the MRCT Center Diversity Workgroup has developed a standard data collection tool (see "Data Variables Tool" in *Toolkit*).

[352] Note, however, that the original ICH signatories were U.S., EU, and Japan.
[353] ICH Harmonized Tripartite Guideline: Ethicic Factors in the Acceptability of Foreign Clinical Data. E5(R1). 5 February 1998.
[354] CDISC CDASH (2017) Clinical Data Acquisition Standards Harmonization: Implementation Guide for Human Clinical Trials Version 2.0. Access via download from CDISC website: https://www.cdisc.org/standards/foundational/cdash/cdashig-v2-0-0 [Accessed 22 June 2020]
[355] Term Suggestion. (2019). Retrieved 20 December 2019, from https://ncitermform.nci.nih.gov/ncitermform/?version=cdisc [Accessed 22 June 2020]

11.3.2 Regulatory guidance on collecting race and ethnicity in the United States

In the U.S., both the FDA[356] and NIH[357] provide guidance on the collection of race and ethnicity data based on the Office of Management (OMB)'s Policy Directive 15.[358] The directive states:

> The racial categories included in the census questionnaire generally reflect a social definition of race recognized in this country and not an attempt to define race biologically, anthropologically, or genetically. In addition, it is recognized that the categories of the race question include race and national origin or sociocultural groups.[359]

These data are based on self-identification across a minimum of five racial groups: (1) American Indian or Alaska Native, (2) Asian, (3) Black or African American, (4) Native Hawaiian or other Pacific Islander, and (5) White. OMB also permits the use a sixth category, (6) "some other race."[360] Respondents may report more than one race.[361] Further, these recommendations also

---

[356] U.S. Food and Drug Administration. (2016). Collection of Race and Ethnicity Data in Clinical Trials.https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf [Accessed 22 June 2020].
[357] NOT-OD-01-053: NIH Policy On Reporting Race And Ethnicity Data: Subjects In Clinical Research. Release Date: August 8, 2001. Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html [Accessed 22 June 2020].
[358] Revisions to the Standards for the Classificiation of Dederal Data on Race and Ethnicity. Executive Office of the President, Office of Management and Budget, October 30, 1997. Available from: https://www.whitehouse.gov/wp-content/uploads/2017/11/Revisions-to-the-Standards-for-the-Classification-of-Federal-Data-on-Race-and-Ethnicity-October30-1997.pdf [Accessed 22 June 2020]
[359] U.S. Census Bureau, Population Estimates Program. Race. 2019. Available from: https://www.census.gov/quickfacts/fact/note/US/RHI425218 [Accessed 22 June 2020]
[360] U.S. Census Bureau, Population Estimates Program. Race. 2019. Available from: https://www.census.gov/quickfacts/fact/note/US/RHI425218 [Accessed 22 June 2020]. In this text, race in the U.S. is defined in the following way: (1) American Indian or Alaska Native. A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment. (2) Asian. A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (3) Black or African American. A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American. (4) Native Hawaiian or Other Pacific Islander. A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. (5) White. A person having origins in any of the original peoples of Europe, the Middle East, or North Africa. Further, Hispanic or Latino is defined as a person of Cuban, Mexican, Puerto Rican, Cuban, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."
[361] U.S. Census 2020, https://2020census.gov/en/about-questions.html. Accessed 22 June 2020.

include two categories for ethnicity: (1) Hispanic or Latino and (2) Not Hispanic or Latino. OMB considers race and ethnicity to be separate concepts. Hispanics and Latinos may be of any race.[362] Because OMB considers ethnicity in these two defined groups of any race, FDA guidance suggests asking the question about ethnicity first, and then proceed to ask about race.[363]

Recently, the rise of genetic and ancestry testing[364] has also spawned an interest in having a more diverse population in clinical research with well-defined racial, ethnic, and ancestral categories (see Chapter 16 "Genetics").[365] While there are additional categories to the ones listed by the OMB for the U.S., there is increased recognition that none are universal. CDISC terminology teams have created a code table mapping file that allows investigators to collect a variety of race and ethnicity identities. In the U.S. these can then be rolled up into the OMB race and ethnicity categories that are required by regulatory agencies (Table 8).[366]

Table 8: CDISC's CDASH version 2.0: Race and ethnicity terminology[367]

ETHNICITY
• **Hispanic or Latino**   ○ *Expanded Categories:* Central American, Cuban, Cuban American, Latin American, Mexican, Mexican American, South American, Spanish • **Not Hispanic or Latino**

[362] Glossary, U.S. Census Bureau, https://www.census.gov/glossary/#term_Ethnicity. [Accessed 22 June 2020]
[363] Department of Health and Human Services. Explanation of Data Standards for Race, Ethnicity, Sex, Primary Language, and Disability. 2011. Available from: https://minorityhealth.hhs.gov/assets/pdf/checked/1/Explanation_of_Draft_Standards.pdf. [Accessed 22 June 2020]
[364] Ramos E, Weissman SM. The dawn of consumer-directed testing. InAmerican Journal of Medical Genetics Part C: Seminars in Medical Genetics 2018 Mar (Vol. 178, No. 1, pp. 89-97).
[365] Popejoy AB, Ritter DI, Crooks K, Currey E, Fullerton SM, Hindorff LA, Koenig B, Ramos EM, Sorokin EP, Wand H, Wright MW. The clinical imperative for inclusivity: Race, ethnicity, and ancestry (REA) in genomics. Human mutation. 2018 Nov;39(11):1713-20.
[366] The code table is an excel sheet listed on this page https://www.cdisc.org/standards/terminology, in the accordion drop down section named "Codetable Mapping Files" and titled "Racec-Ethnicc Codetable." And content is based on published terminology so is updated as they add more race and ethnic terminology to the codelists.
[367] See Standards, Foundational, CDASH, CDASH2.0 at https://www.cdisc.org/standards/foundational/cdash/cdashig-v2-0-0 [Accessed 22 June 2020]

- **Not Reported**

RACE

- **American Indian or Alaska Native**
  - *Expanded categories*: Alaska Native, American Indian, Caribbean Indian, Central American Indian, Greenland Inuit, Nupiat Inuit, Siberian Eskimo, South American Indian, Yupik Eskimo
- **Asian**
  - *Expanded categories*: Asian American, Bangladeshi, Bhutanese, Burmese, Cambodian, Chinese, Filipino, Hmong, Indonesian, Iwo Jiman, Japanese, Korean, Laotian, Malagasy, Malaysian, Maldivian, Mongolian, Nepalese, Okinawn, Pakistani, Singaporean, Sri Lankan, Taiwanese, Thai, Vietnamese
- **Black or African American**
  - *Expanded categories*: African, African American, African Caribbean, Bahamian, Barbadian, Black Central American, Black South American, Batswana, Dominica Islander, Dominican, Ethiopian, Haitian, Jamaican, Liberian, Malagasy, Namibian, Nigerian, Trinidadian, West Indian, Zairean
- **Native Hawaiian or Other Pacific Islander**
  - *Expanded categories*: Melanesian, Micronesian, Polynesian
- **White**
  - *Expanded categories*: Arab, Eastern European, European, Mediterranean, Middle Eastern, North American, Northern European, Russian, Western European, White Caribbean, White Central American, White South American
- **Other Race**

As part of its data collection and improvement process, Kaiser Permanente, one of the largest not-for-profit health systems in the U.S., developed more granular categories of ethnicity in addition to the standard OMB categories. These categories are based on personal self-identification and are meant to reflect the effects of globalization, population displacement,

and social movements.[368] They have not, however, been more widely adopted for clinical research demographic classification.

11.3.3 Regulatory guidance on reporting race and ethnicity categories in ex-U.S. regions

There is no consistency in the collection of race and ethnicity globally. Ethnic classification systems are typically constructed by history and culture and specific to the country or region itself.

The ICH E5 (R1)[369] provides some guidance on how to develop strategies around ethnic factor considerations [370] to allow for adequate evaluation by regulatory agencies. The EMA and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) both refer to this document in their regulatory guidance around the question of ethnicity. Examples of country and/or region-specific classification systems include:

- Japan's **PMDA** refers broadly to two categories (i.e., Japanese, non-Japanese) in informational guidance[371] and more specifically recognizes the CDISC race/ethnicity-controlled terminology (CT) code list.[372]

- A report from the **European Commission** provides a comprehensive analysis on data collection in the field of ethnicity.[373] It recognizes the legal and regulatory complexities

[368] G. Kaiser Permanente: Evolution of Data Collection on Race, Ethnicity, and Language Preference Information. (2014, October02). Retrieved from https://www.ahrq.gov/research/findings/final-reports/iomracereport/reldataapg.html [Accessed 22 June 2020]
[369] *Ethnic Factors in the Acceptability of Foreign Clinical Data : ICH*. (2019). *Ich.org*. Retrieved 20 September 2019, from https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf [Accessed 22 June 2020]
[370] ICH E5(R1) defines ethnic factors as those relating to the genetic and physiologic (intrinsic) and the cultural and environmental (extrinsic) characteristics of a population.
[371] Basic principles on Global Clinical Trials. Informational translation by PMDA of the final notification published in Jananese on Sept. 28th 2007. https://www.pmda.go.jp/files/000153265.pdf [Accessed 22 June 2020]
[372] Technical Conformance Guide on Electronic Study Data Submissions. Provisional Translation by PMDA (as of July 2015). https://www.pmda.go.jp/files/000206449.pdf [Accessed 22 June 2020.]
[373] Farkas L. Analysis and comparative review of equality data collection practices in the European Union: Data collection in the field of ethnicity. Directorate-General for Justice and Consumers Directorate D–Equality Unit JUST D. 2017;1. http://ec.europa.eu/newsroom/just/document.cfm?action=display&doc_id=45791 [Accessed 22 June 2020]

associated with collecting ethnicity data within each of the member states. There are different legal and statistical categories that denote racial and ethnic origin in EU surveys. The categories can include: racial origin, ethnic origin, descent, citizenship, place of birth, place of birth of parents, nationality, religion, language, and geographic origin.

- The **Australian** Standard Classification of Cultural and Ethnic Groups (ASCCEG) provides statistical standards for data classification related to the ethnic and cultural composition of the Australian Population.[374] ASCCEG considers ethnicity as a multi-dimensional concept that is based on self-perceived group identification using several distinctive characteristics. These include geographic proximity of cultural and ethnic groups in terms of the location in which they originated and other social and cultural characteristics such as languages spoken and religious practices. The ASCCEG website states that:

  > The classification is not intended to classify people, but rather to classify all claims of association with a cultural or ethnic group.[375]

  The ASCCEG has a three-level hierarchical structure that consists of cultural and ethnic groups, that are then rolled up into narrow groups, and subsequently aggregated into one of nine broader, major categories: 1) Oceanian, 2) North-West European, 3) Southern and Eastern European, 4) North African and Middle Eastern, 5) South-East Asian, 6) North-East Asian, 7) Southern and Central Asian, 8) Peoples of the Americas, and 9) Sub-Saharan African.[376]

- **Statistics Canada** provides a definition for ethnic origin that is "the ethnic or cultural origins of a person's ancestors. An ancestor is usually more distant than a grandparent."[377] Statistics Canada further provides a list of 8 ethnic origins that include 1) North American

[374] *1249.0 - Australian Standard Classification of Cultural and Ethnic Groups (ASCCEG), 2016*. (2019). *Abs.gov.au*. Retrieved from https://www.abs.gov.au/ausstats/abs@.nsf/mf/1249.0 [Accessed 22 June 2020]
[375] 1249.0 - Australian Standard Classification of Cultural and Ethnic Groups (ASCCEG), 2016. (2019). Abs.gov.au. Retrieved from: https://www.abs.gov.au/ausstats/abs@.nsf/mf/1249.0 [Accessed 22 June 2020]
[376] 1249.0 - Australian Standard Classification of Cultural and Ethnic Groups (ASCCEG), 2016. (2019). Abs.gov.au. Retrieved from https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1249.02016?OpenDocument
[377] Ethnic origin of person. (2019). Www23.statcan.gc.ca. Retrieved 26 September 2019, from http://www23.statcan.gc.ca/imdb/p3Var.pl?Function=DEC&Id=103475 [Accessed 22 June 2020]

Aboriginal origins, 2) Other North American origins, 3) European origins, 4) Caribbean origins, 5) Latin, Central and South American origins, 6) African origins, 7) Asian origins, and 8) Oceania origins.[378]

- The regulations in data collection and reporting with regards to race and ethnicity in other regions, including **Africa, Asia, and South America**, are not explicit and may be related to the considerable heterogeneity of classifications that exist within and between the countries.

11.4 Sex and gender

The terms sex and gender are often used interchangeably, even though these terms are distinct. This Diversity Framework draws upon the World Health Organization (WHO) definition of **"**Sex**"** as the different physiological and biological characteristics of males and females, such as reproductive organs, chromosomes, hormones, etc.[379] "Gender" is defined as "refer[ing] to the socially constructed characteristics of women and men – such as norms, roles and relationships of and between groups of women and men." It varies from society to society and can, both in society and for the individual, evolve over time.[380] The concept of gender includes five important elements: relational, hierarchical, historical, contextual and institutional.[381] The definitions of sex and gender put forth by other federal and regulatory agencies vary and are summarized in Table 9 below.

[378] List of ethnic origins 2016. (2017). Www23.statcan.gc.ca. Retrieved 26 September 2019, from http://www23.statcan.gc.ca/imdb/p3VD.pl?Function=getVD&TVD=402936
[379] (2015, May 14). Glossary of terms and tools. Retrieved from https://www.who.int/gender-equity-rights/knowledge/glossary/en/ [Accessed 22 June 2020]
[380] See also http://www.equaldex.com. [Accessed 5 July 2020]
[381] (2015, May 14). Glossary of terms and tools. Retrieved from https://www.who.int/gender-equity-rights/knowledge/glossary/en/ [Accessed 22 June 2020]

Table 9: Definitions of sex and gender in U.S. federal agencies, ICH, and WHO

ORGANIZATION/AGENCY	SEX DEFINED AS:	GENDER DEFINED AS:
NIH/ORWH Definition[382]	Biological differences between females and males, including chromosomes, sex organs, and endogenous hormonal profiles.	Socially constructed and enacted roles and behaviors which occur in a historical and cultural context and vary across societies and over time.
Institute of Medicine (IOM) Definition referenced by FDA[383]	The classification of living things, generally as male or female according to their reproductive organs and functions assigned by chromosomal complement.	A person's self-representation as male or female, or how that person is responded to by social institutions based on the individual's gender presentation. Gender is rooted in biology, and shaped by environment and experience.
ICH of Technical Requirements for Registration of	The biogenetic differences that distinguish males and females.	The array of socially constructed roles and relationships, behaviors and values that society ascribes to two sexes on a differentiated basis.

[382] National Institutes of Health. Sex and Gender. Retrieved from https://orwh.od.nih.gov/sex-gender. [Accessed 22 June 2020]
[383] U.S. Food and Drug Administration. Collection of Race and Ethnicity Data in Clinical Trials. October 2016. Retrieved from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/collection-race-and-ethnicity-data-clinical-trials. [Accessed 22 June 2020]

Pharmaceuticals for Human Use		
WHO Definition[384]	The different physiological and biological characteristics of males and females, such as reproductive organs, chromosomes, hormones, etc.	The socially constructed characteristics of women and men – such as norms, roles and relationships of and between groups of women and men. It varies from society to society and can be changed.
NIH/NIMHD	**Sexual and Gender Minority (SGM):** SGM populations include, but are not limited to, individuals who identify as lesbian, gay, bisexual, asexual, transgender, two-spirit, queer, and/or intersex. Individuals with same-sex or same-gender attractions or behaviors and those with a difference in sex development are also included. These populations also encompass those who do not self-identify with one of these terms but whose sexual orientation, gender identity or expression, or reproductive development is characterized by non-binary constructs of sexual orientation, gender, and/or sex.	

[384] World Health Organizaation. Glossary of terms and tools. Accessible at https://www.who.int/gender-equity-rights/knowledge/glossary/en/. [Accessed 22 June 2020]

A comprehensive study by Hankivsky et al.[385] systematically explored statements about sex and gender considerations in research at national-level funding agencies from the EU, North America, and Australia as well as top-ranked scientific journals. Their results illustrate discrepancies in conceptualization and inclusion/exclusion criteria of sex and gender in research. Further, the authors assert that a paradigm shift is necessary to: (1) recognize and understand how sex and gender covary with other demographic/non-demographic categories (e.g., race, socioeconomic status, geographic location) that impact health; and (2) that research should not assume that "sex" can be separated from "gender."

Attention to the inclusion, analysis, and results reporting of sex and gender in biomedical research has expanded the understanding of these factors in drug development and health outcomes.[386] Heidari et al. [387] published the Sex and Gender Equity in Research (SAGER) guidelines to highlight the importance of distinguishing sex and gender information in study design, analyses, results, and interpretation in clinical research. The guidelines advise researchers, investigators, and authors to be mindful when using the terms "Sex" and "Gender" and to delineate between the two to avoid confusion. The SAGER guidelines are not yet adopted internationally. The Lancet also issued similar editorial guidelines for sex and gender analysis for journal editors, reviewers and authors.[388] The guidelines require clear, concise, and discrete reporting and assessment of sex and gender variables.

11.4.1 Data standards for collecting sex and gender information

CDISC offers a controlled terminology code list (labelled "SEX") that is accepted by the FDA and other regulatory agencies, and includes:

[385] Hankivsky O, Springer KW, Hunting G. Beyond sex and gender difference in funding and reporting of health research. Research integrity and peer review. 2018 Dec;3(1):6.
[386] Gahagan J, Gray K, Whynacht A. Sex and gender matter in health research: addressing health inequities in health research reporting. International Journal for equity in health. 2015 Dec;14(1):12.
[387] Heidari S, Babor TF, De Castro P, Tort S, Curno M. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. Research Integrity and Peer Review. 2016 Dec;1(1):2.
[388] Schiebinger L, Leopold SS, Miller VM. Editorial policies for sex and gender analysis. Lancet (London, England). 2016 Dec 10;388(10062):2841.

SEX:

- ☐ M-male
- ☐ F-female
- ☐ U-unknown
- ☐ Undifferentiated

Importantly, since the terms sex and gender are often used interchangeably, what is often captured and analyzed as "gender" is the information specific to "sex."[389] Study sponsors should specify the appropriate definition during data collection to ensure accurate study data collection.

Expression of gender and its terminology are evolving and are culturally sensitive. In some countries, any expression of gender or belief other than heterosexuality, predicated on binary gender stereotypes, is criminalized.[390,391] Identification as gender-nonconforming may be problematic, if not illegal; cultural, societal, and political norms must be taken into account. Because collection of gender data can be not only sensitive but also subject to legal sanction, the importance of gender on biology (and heterogeneity of treatment effect) should be determined early in protocol development. Further, individuals who have non-conforming gender identities often cross the intersection of race/ethnicity with sex/gender sensitivities (see Section 2.3 "Defining diversity" and Figure 4 "Dimensions of diversity are not independent variables.") Staff should be aware of this further complexity. CDISC has not created data collection standards for gender; other models, however, have been developed and are in use (Table 10):

[389] Clayton JA, Tannenbaum C. Reporting sex, gender, or both in clinical research?. Jama. 2016 Nov 8;316(18):1863-4.
[390] See for instance, Human Dignity Trust. Map of countries that criminalise LGBT people. Available at: https://www.humandignitytrust.org/lgbt-the-law/map-of-criminalisation/. [Accessed 22 June 2020.]
[391] See Human Rights Watch. #Outlawed. "The love that dare not speak its name." Available at http://internap.hrw.org/features/features/lgbt_laws/. [Accessed 22 June 2020.]

Table 10: Examples of models capturing gender categories

ORGANIZATION	GENDER CATEGORIES
Statistics Canada	☐ Male Gender ☐ Female Gender ☐ Gender Diverse "Indeterminate" or Unknown or Left-Open
Bauer, G., Braimoh, J., Scheim, A., & Dharma, C. (2017). Transgender-inclusive measures of sex/gender for population surveys: Mixed-methods evaluation and recommendations. *PLOS ONE*, *12*(5), e0178043. doi:10.1371/journal.pone.0178043	☐ Male Gender ☐ Female Gender ☐ Trans-male/Trans man ☐ Trans-female/ Trans woman ☐ Genderqueer/Gender non-conforming ☐ Different Identity: Please specify_____

Future work is necessary to standardize data collection fields and variables for gender and gender identity in order to understand their influence and impact on health, disease, and treatment.

In order to facilitate consistent data collection of clinical research demographic and non-demographic data, the MRCT Center Diversity Workgroup has developed a standard data collection tool (see "Data Variables Tool" in *Toolkit*). We offer this tool now as an interim measure, but we suggest that an international consensus be developed for the collection and reporting of this information with representation from the appropriate populations.

11.5 Social determinants of health

If something is not measured, its role in explaining heterogeneity of effect cannot be understood. The broad term "Social Determinants of Health (SDH)" includes economic and educational attainment, diet (nutrition, food choice), food and housing security/insecurity, availability of affordable health care, presence of stress, exposure to violence, and others. The World Health Organization,[392] Healthy People 2020,[393] and the Centers for Medicaid and Medicare Services[394] have put forth frameworks to standardize SDH elements, but none are universally accepted (or necessarily globally appropriate) and none routinely collected. Further, collecting these measures takes time, may provoke discomfort on the part of participants and practitioners/investigators,[395] and, in the absence of meaningful analysis and interpretation in the context of clinical trials, have not been prioritized for collection in clinical trials.

Socio-economic status (SES), one of the most prominent components of SDH, is not uniformly requested or collected in a clinical research or clinical trial setting. In observational studies, questions vary depending upon the nature of the study and may include income, education and occupation. There is no universal standard as to how SES questions are asked nor an understanding about whether asking the questions differently or in a different order may elicit different responses. The National Committee on Vital and Health Statistics identified five indicators as a measure of SES:[396] income, education, occupation, family size, and household composition. Income may not be a good international indicator of SES since it does not reflect net assets, buying power, or community status. As such, wealth may be a better indicator but is

[392] Social determinants of health. (2019). World Health Organization. Retrieved 11 November 2019, from https://www.who.int/social_determinants/en/ [Accessed 22 June 2020]
[393] Social Determinants of Health. Retrieved from https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health [Accessed 22 June 2020]
[394] Centers for Medicaid and Medicare Services. The Accountable Health Communities Health-Related Social Needs Screening Tool. Available at: https://innovation.cms.gov/Files/worksheets/ahcm-screeningtool.pdf. [Accessed 22 June 2020]
[395] Garg A, Boynton-Jarrett R, Dworkin PH. Avoiding the unintended consequences of screening for social determinants of health. JAMA 2016 Aug 23;316(8):813-4.
[396] Queen, S. (2012, August). Assessing the Potential for Standardization of Socioeconomic Status in HHS Surveys. In *2012 National Conference on Health Statistics Washington DC*. Available at: https://www.cdc.gov/nchs/ppt/nchs2012/SS-34_QUEEN.pptx. [Accessed 22 June 2020].

more challenging to ascertain. The time and cost associated with collecting wealth indicators—as well as its personal sensitivity—constrains its use in clinical research globally.

A recent observational study utilized data from the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attach Trial (ALLHAT) to determine whether differences in socio-economic status affected clinical outcomes from antihypertensive therapy.[397] The results demonstrated that in spite of standardized treatment protocols, ALLHAT participants in the lowest-income locations faced poorer blood pressure control and worse adverse cardiovascular events, underscoring the need to measure socio-economic status in the design of randomized control trials.

The challenge of collecting SDH in clinical trials is underscored by parallel efforts in clinical care settings. In 2018, The American College of Physicians published a set of policy recommendations to better integrate social determinants of health into the healthcare system.[398] The recommendations highlighted the need for public policies that address environmental, geographical, occupational, educational, and nutritional social determinants of health and the role of SDH data to aid "evidence-driven decision making." The experience in clinical care settings may inform clinical research.

In the U.S., the National Association of Community Health Centers and its partners undertook a nationwide effort to develop the Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences (PRAPARE) toolkit[399] to help health centers and other providers collect and apply data to better understand a patient's SDH. The PRAPARE toolkit provides a core set of measures as well as a standardized list of questions that capture socioeconomic and environmental needs and circumstances.

[397] Shahu A, Herrin J, Dhruva SS, Desai NR, Davis BR, Krumholz HM, Spatz ES. Disparities in socioeconomic context and association with blood pressure control and cardiovascular outcomes in ALLHAT. Journal of the American Heart Association. 2019 Aug 6;8(15):e012277.
[398] Daniel H, Bornstein SS, Kane GC. Addressing social determinants to improve patient care and promote health equity: an American College of Physicians position paper. Annals of internal medicine. 2018 Apr 17;168(8):577-8.
[399] National Association of Community Health Centers. PRAPARE: Protocol for Responding to and Assessing Patient's Assets, Risks, and Experiences: PRAPARE Implementation and Action Toolkit.. Available at: http://www.nachc.org/research-and-data/prapare/toolkit/ and About the PRAPARE Assessement Tool. Available at: http://www.nachc.org/research-and-data/prapare/about-the-prapare-assessment-tool/. [Accessed 22 June 2020]

11.5.1 Data standards for collecting social determinants of health in clinical trials

To date, no clear data standards have been developed to collect SDH and/or SES in clinical research. Given the increased attention to the impact of low SDH on clinical outcomes, there is an opportunity to create a framework for consistent data collection and furthermore to build the evidence base describing the impacts of SDH on response treatment. Further empirical research is necessary. Tools such as the PRAPARE toolkit provide a framework for data collection of SDH, for academic medical centers and sponsors to work with when designing clinical trials or prospective research studies.

11.6 Recommendations: Collection and reporting of data variables

The overall strategy for data collection and reporting will be protocol-specific and will depend on the disease or condition being studied. Sponsors and Investigators should carefully consider the biological significance related to the intrinsic and extrinsic factors collected as part of the research and plan collection of variables accordingly.[400] In order to facilitate consistent data collection of clinical research demographic and non-demographic data, the MRCT Center Diversity Workgroup has developed a standard data collection tool (see "Data Variables Tool" in *Toolkit*).

[400] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline. Ethnic factors in the acceptability of foreign clinical data E5(R1). 5 February 1998. Available at: https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf [Accessed 22 June 2020.]

OVERALL STRATEGIES FOR DATA VARIABLE COLLECTION AND REPORTING	
Data Variable Collection	• Determine the critical demographic and non-demographic variables to collect as part of clinical research. This will depend on the disease or condition being studied. • Provide justification in the protocol for any sub-group (demographic/non-demographic) that will be excluded. • Collect demographic and non-demographic variables according to CDISC standards, as available. In the absence of CDISC standards, collect data at the most granular level possible. • Gain worldwide consensus on the determination and collection of demographic variables that accurately represent specific racial and ethnic classification systems of those regions. • Retain variables at the most granular level throughout data analysis for future/potential individual patient data submission and/or analysis. • Future work is necessary to standardize data collection fields and variables for gender and social determinants of health.

Data Variable Reporting	• Establish common data collection and reporting methods to ensure data can be compared, and meta-analyses performed. Typically, health regulatory authorities and sometimes funders will establish those standards. • As available, utilize the specific requirements of the national regulatory authority (e.g., FDA, PMDA) for data element reporting. • As needed and/or in the absence of regulatory requirements/guidance, determine and rationalize discrete groupings for reporting variables. Sponsors can utilize country-specific liaisons for these data. In the absence of a country-specific liaison, national regulatory agencies can be contacted. • All reported variables should be accompanied by a clear data dictionary, methods for collection, and units of measure.

12. Approach to Data Analysis

Regulatory approvals for investigational products are typically based on carefully designed, double-blind, randomized controlled clinical trials. Ideally, the participant population enrolled in clinical trials reflects the composition of the general population or of those affected by the disease, so that the research yields generalizable knowledge pertinent to the population that will use the product. As the benefits and risks of drugs and biologics can vary depending on demographics, comorbidities, genetic differences, and other intrinsic and extrinsic factors, clinical trials might also provide information that informs the use of new therapeutic agents within pre-specified subgroups.[401,402,403] Ideally one would like to know the benefit and risk of every product in every conceivable subgroup—thereby promoting data-driven choices that offer the greatest benefit and least risk for every patient, but this of course cannot be done with the limited statistical power in subgroups of participants.[404] Powering a study to elucidate differences, or to provide affirmative evidence of benefit and safety, for different subgroups would result in larger sample sizes, costs, study duration, and delay to regulatory review and approval. Were a clinical trial required to have sufficient sample size to have adequate power for within-subgroup analysis, the overall sample size would be overpowered to examine the primary objective of the trial. This is true even when the subgroups of interest comprise relatively large proportions of the overall population (e.g., sex, region), but becomes far more challenging for less common subgroups.[405] However, enrolling a diverse population provides the best opportunity for an informed analysis of important subgroups, illuminating potential signals of disproportionate benefit or risk that would then lead to additional formal study, post-approval monitoring, or directed analyses using observational data and real-world evidence

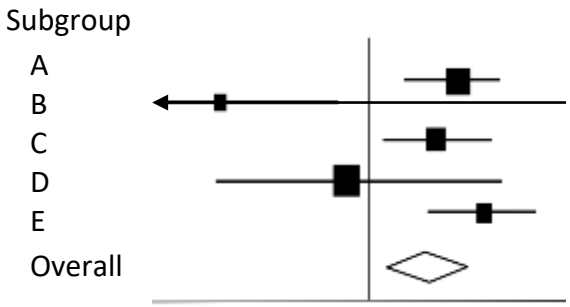
[401] Snapinn S, Jiang Q. Choice of Metrics and Other Considerations for Benefit-Risk Analysis in Subgroups. Benefit-Risk Assessment Methods in Drug Development: Bridging Qualitative and Quantitative Assessments. 2016 May 25:105-15.
[402] LaVange LM. Statistics at FDA: Reflections on the Past Six Years. Statistics in Biopharmaceutical Research. 2019 Jan 2;11(1):1-2.
[403] Lazar AA, Bonetti M, Cole BF, Yip WK, Gelber RD. Identifying treatment effect heterogeneity in clinical trials using subpopulations of events: STEPP. Clinical Trials. 2016 Apr;13(2):169-79.
[404] The role of real world data and real world evidence is discussed elsewhere. Here we discuss subgroup analysis in clinical trials.
[405] Li G, Taljaard M, Van den Heuvel ER, Levine MA, Cook DJ, Wells GA, Devereaux PJ, Thabane L. An introduction to multiplicity issues in clinical trials: the what, why, when and how. International journal of epidemiology. 2016 Dec 26;46(2):746-55.

(see Section 12.4 "Real World Data (RWD), Real World Evidence (RWE), and observational data").

12.1 Traditional approaches to subgroup analysis

The traditional approach for interpreting subgroup analyses (for efficacy)[406] is best described as ruling out inconsistencies. Specifically, there is an *a priori* assumption that the treatment is equally effective in all subgroups, and the subgroup analyses are examined to see whether there is substantial evidence to the contrary. What constitutes substantial evidence is not generally specified. In many publications, for instance, a forest plot[407] (see Figure 26) is provided that shows the results of subgroup analyses, including the point estimate for the magnitude of the treatment effect (i.e., effect size) and its confidence interval:

Figure 26: Example of forest plot



In this example, the vertical line represents no effect. The boxes represent individual subgroups, the size of the box reflecting the number of participants in the subgroup and the horizontal line represents the confidence interval of each subgroup. The open triangle represents the analysis of the entire trial (ie., subgroups A through E combined). The overall confidence interval does not cross the vertical line (i.e., no effect), indicating that the overall result is statistically significant. The only two point estimates that fall to the left of the vertical line have wide

[406] For subgroup analyses of safety, unlike efficacy, conclusions are generally based on simple differences.
[407] A forest plot, originally used to present the results of a meta-analysis of randomized clinical trials, is a graphical representation that compares multiple analyses of the same outcome and is now used to evaluate the consistency of a treatment effect across subgroups. The vertical line in the center represents no effect (and is therefore equal to 1 if an odds ratio or relative risk and zero if a mean difference). The horizontal bar represents the confidence interval, and the greater or longer the horizontal bar, the greater the uncertainty of the result. If the horizontal bar (i.e., confidence interval) crosses the vertical bar, the data are consistent with the null hypothesis for that analysis.

confidence intervals due to small sample sizes. Therefore, the overall effect size estimate appears to be a reasonable estimate in any subgroup.[408]

In some cases, the subgroup analyses are examined informally (i.e., without hypothesis tests), in which case the interpretation is subjective. In other cases, the interpretation is guided by statistical tests of interaction that determine whether there is statistical evidence that the variation in the magnitude of effect across levels of a subgroup is more than would be expected by chance alone. However, these tests are just a guide, in part because of the issue of multiplicity[409] and the lack of power: since many subgroups are examined, the possibility of type 1 error (the rejection of a true null hypothesis, also termed a "false positive")[410] can be high. In addition, the power of the test of interaction is typically low to detect clinically meaningful interactions. Even if differences in the magnitude of the effect are found, differences in magnitude are less important than differences in direction. This is typically highlighted as the difference of "quantitative" versus "qualitative" (differences in direction) interactions.[411] That is, it is less problematic when a treatment works in all subgroups, but less well in some than in others, than it is when the treatment is beneficial in some subgroups and harmful in others.[412] In other words, given that the ultimate issue is not the population response but that of the individual needing therapy, and individual responses are highly variable, does it matter *whether* it "worked" or *how well* it "worked"?

The assumption that a treatment is equally efficacious in all subgroups is probably not a reasonable assumption in that the absence of evidence of inconsistency does not equate to evidence of absence of inconsistency in treatment response. Further, this traditional approach

[408] Cochrane UK. How to read a forest plot. Available at: https://uk.cochrane.org/news/how-read-forest-plot. [Accessed 22 June 20].
[409] When multiple tests of hypotheses are performed within one randomized clinical trial, the likelihood that there will be an increase in the risk of a false positive is increased. If, for instance, one accepts a significance level of p=0.05 (a 5% error rate or 1 in 20 tests may be falsely positive, but one performs 5 tests on the same dataset, the likelihood that one of those five will be falsely positive increases to 23% ("5 shots on goal, not one"). Statistical adjustments must be made for multiple testing,
[410] A type I error is the rejection of a true null hypothesis (a "false positive"), while a type II error is the acceptance of a false null hypothesis (a "false negative").
[411] See also: Lin J, Bunn V, Liu R. Practical Considerations for Subgroups Quantification, Selection and Adaptive Enrichment in Confirmatory Trials. Statistics in Biopharmaceutical Research. 2019 Oct 2;11(4):407-18.
[412] For this reason, a test for *quantitative* interaction (i.e., the standard test for interaction) will often be followed by a test for *qualitative* interaction (which specifically tests for the latter situation).

provides no guidance on the desired sample sizes for the subgroups.[413] The larger the subgroup, the more meaningful and informative the analysis. However, given that the sponsor can rely on the assumption of consistency in treatment response, there is no incentive to enroll a diverse population particularly as the primary scientific objective is to reach the primary endpoint (and in the shortest time possible). Indeed, it may even be preferable to maintain wide confidence intervals so that there is no challenge to efficacy in one subgroup or another. In addition, as difficult as it is to identify inconsistency between subgroups (i.e., distinguish between random variation and true variation) when the populations are large (e.g., men versus women), it is far more difficult when the populations are small (i.e., small racial or ethnic groups, small countries, regions within a country, etc.).

Because of this, skeptics of the value of inclusion argue that in the absence of the statistical ability to discern differences, attention to inclusion of diverse populations should be a secondary focus of scientific inquiry, if a focus at all. However, how can any understanding of subpopulations—and most importantly of the individual being treated—be obtained if never studied?[414,415] Optimally, the study should be prospectively designed to analyze differences in responsiveness across subpopulations, and post hoc analysis would not be necessary. Given the tension between time to primary endpoint and understanding heterogeneity of treatment effect across subgroups, additional methods are needed to discern when a clinically significant difference impacting biological responsiveness—and safety—may exist in a subgroup.

As discussed, a number of variables are (largely) categorical (e.g., male versus female) and comparison of outcomes between the variables is meaningful and should routinely be performed and reported. The form of reporting should be standardized so that the analysis can be understood, repeated, and the confidence interval appreciated. Many variables are not categorical and are continuous (e.g., age) or differentiated inconsistently across settings (e.g., ethnicity). In these instances, a decision must be made as to the approach to analysis. Ideally,

[413] Currently, typically the sizes of subgroups are not specified even if we had enough patients unless a restricted stratified design is employed.
[414] Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet. 2005; 365(9454): 176- 186.
[415] Altman DG. Clinical trials: Subgroup analyses in randomized trials—more rigour needed. Nature. Reviews Clinical Oncology. 2015 Sep;12(9):506.

analysis of a continuous variable such as age would be most informative if one could conclude the relationship of the variable to response (e.g., the benefit of drug A increased by X% for each year of age). However, that analysis requires one to know the functional form of the relationship between response and the variable (i.e., is it linear as in this example, or is it quadratic, log-linear, or other). Partitioning variables into discrete and nonoverlapping groups (e.g., 18-39 years old, 40-64 years old, ≥65 years old)[416] allows comparisons that are meaningful but may be less informative.

In clinical research, there may be more complex and subtle interactions that go beyond simply subgroup differences. This issue of intersectionality should be addressed. In other words, a person is not just the sum of multiple demographic variables, but rather their intersection. Each individual domain (age, gender, ethnicity, sexual orientation, etc.) may have a different effect when paired with one or more other domains: e.g., a homosexual Black woman may differ in terms of key outcomes from a heterosexual Black woman, or from a homosexual White woman, or a heterosexual Black man, etc.). This complicates the issue of subgroup analysis, since there are interactions, not just a range of separate main effects.[417] The statistical treatment of "intersectionality" involves, at least in part, tests of interaction (e.g., multivariate risk scores) that adds additional complexity to subgroup analysis.

[416] Age is also often characterized categorically for practicality. Dosing is typically adjusted on account of drug metabolism (e.g., renal or hepatic impairment), not age. Additionally, products are usually available in a discrete number of formulations.

[417] Importantly, the issue of complexity and intersectionality applies to the individual prospective patient (who represents a unique intersection of multiple subgroups) and the challenge of extrapolating the results of a clinical trial to decide whether or not that individual would benefit from and should take a drug product.

12.2 Novel approaches to subgroup analysis

Multiple approaches have been suggested for subgroup analysis.[418,419,420,421] And, as mentioned, while it may be possible to perform some analyses when the sample is intrinsically large (e.g., men versus women), small subgroup populations do not allow for robust analyses; interpretations of any differences are not, therefore, decisive.[422, 423, 424] Reasonably, the question of absence of inconsistency could, and arguably should, be changed to an *estimate* of the level of heterogeneity (differences) among subgroups. The challenge then would become (1) how to estimate heterogeneity of treatment effect (HTE), and (2) the parameters for acceptable differences in HTE, and that in turn may depend upon a number of factors (e.g., unmet medical need, effect size, safety relative to efficacy).

The issues of the type and methods of subgroup analysis are a threshold statistical challenge. First, whether the subgroup itself is a categorical (e.g., sex), continuous (e.g., age), or other (e.g., comorbidity) variable will impact the analysis. Methodologies that begin to give affirmative evidence of treatment heterogeneity between subgroups should be further explored, rather than continuing to assume a lack of evidence for meaningful heterogeneity.[425] One basic approach would be a Bayesian hierarchical model[426] where the prior belief that the

[418] Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet. 2000; 355(9209): 1064- 106.
[419] Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine—reporting of subgroup analyses in clinical trials. New England Journal of Medicine. 2007 Nov 22;357(21):2189-94.
[420] Pocock SJ, McMurray JJ, Collier TJ. Statistical controversies in reporting of clinical trials: part 2 of a 4-part series on statistics for clinical trials. Journal of the American College of Cardiology. 2015 Dec 15;66(23):2648-62.
[421] Brankovic M, Kardys I, Steyerberg EW, Lemeshow S, Markovic M, Rizopoulos D, Boersma E. Understanding of interaction (subgroup) analysis in clinical trials. European journal of clinical investigation. 2019 May 28:e13145.
[422] Hernandez AV, Boersma E, Murray GD, Habbema JD, Steyerberg EW. Subgroup analyses in therapeutic cardiovascular clinical trials: are most of them misleading? Am Heart J. 2006; 151(2): 257- 264.
[423] Lagakos SW. The challenge of subgroup analyses–reporting without distorting. N Engl J Med. 2006; 354(16): 1667- 1669.
[424] Wallach JD, Sullivan PG, Trepanowski JF, Sainani KL, Steyerberg EW, Ioannidis JP. Evaluation of evidence of statistical support and corroboration of subgroup claims in randomized clinical trials. JAMA Intern Med. 2017; 177(4): 554- 560.
[425] Wallach JD, Sullivan PG, Trepanowski JF, Steyerberg EW, Ioannidis JP. Sex based subgroup differences in randomized controlled trials: empirical evidence from Cochrane meta-analyses. bmj. 2016 Nov 24;355:i5826.
[426] Bayesian hierarchical modeling is a statistical approach to make scientific inferences about a population. As a Bayesian model, it combines prior information on the model parameters with observed data to determine a

results are consistent across subgroups is modified by the data themselves. Such a model could provide, within any subgroup, an estimate of the magnitude of the treatment effect as well as a measure of the strength of evidence for a positive treatment effect.[427,428,429,430,431,432] Along with criteria for deciding whether or not the results are adequate to conclude efficacy within a subgroup, Bayesian models help to provide a basis for choosing optimal subgroup sample sizes[433, 434] and therefore provide a scientific basis to enroll a diverse population. However, the assumptions in Bayesian methods must be prespecified and may still be questioned: while it is reasonable to assume that a 17-year old will be more similar to a 25-year old than an 85-year old, and, and that Norwegians will be more similar to Swedes than to Japanese, the question is how much to "borrow" from one set of observations to another. The amount of "borrowing" may need to be prespecified, lest the amount borrowed is simply chosen to "fit" the result once obtained. The degree of borrowing will depend upon the specific scientific situation but the process for doing this must be agreed upon and prespecified. Standardization, if possible, will also simplify the approach and comparisons across different analyses. The Bayesian approach is mathematically complex but worthy of further development.

posterior distribution, and as a hierarchical model it involves multiple levels. In the context of subgroup analyses, this model is used to "shrink" the estimate of the treatment effect within any subgroup toward the estimated treatment effect based on the clinical trial as a whole.

[427] Berry DA. Bayesian clinical trials. Nature reviews Drug discovery. 2006 Jan;5(1):27.

[428] Quintana M, Viele K, Lewis RJ. Bayesian analysis: using prior information to interpret the results of clinical trials. Jama. 2017 Oct 24;318(16):1605-6.

[429] Yin G, Lam CK, Shi H. Bayesian randomized clinical trials: From fixed to adaptive design. Contemporary clinical trials. 2017 Aug 1;59:77-86.

[430] Friede T, Posch M, Zohar S, Alberti C, Benda N, Comets E, Day S, Dmitrienko A, Graf A, Günhan BK, Hee SW. Recent advances in methodology for clinical trials in small populations: the InSPiRe project. Orphanet journal of rare diseases. 2018 Dec 1;13(1):186.

[431] LaVange LM. Statistics at FDA: Reflections on the Past Six Years. Statistics in Biopharmaceutical Research. 2019 Jan 2;11(1):1-2.

[432] VanderWeele TJ, Luedtke AR, van der Laan MJ, Kessler RC. Selecting optimal subgroups for treatment using many covariates. Epidemiology. 2019 May 1;30(3):334-41.

[433] Ondra T, Dmitrienko A, Friede T, Graf A, Miller F, Stallard N, Posch M. Methods for identification and confirmation of targeted subgroups in clinical trials: a systematic review. Journal of biopharmaceutical statistics. 2016 Jan 2;26(1):99-119.

[434] West BT, Wagner J, Coffey S, Elliott MR. The Elicitation of Prior Distributions for Bayesian Responsive Survey Design: Historical Data Analysis vs. Literature Review. arXiv preprint arXiv:1907.06560. 2019 Jul 15.

One central scientific question is how best to establish decision criteria to determine when meaningful differences between subgroups exist, thereby decreasing the subjectivity of conclusions drawn from the data. Additional questions relate to whether subgroup analyses must always be pre-planned (rather than determined based on an initial review of the data and observed results) and when *post-hoc* subgroup analyses could be performed, even if explicitly stated as such.[435] For the traditional approach to analysis, reporting standards must be developed, including expectations that (1) the methods are described, (2) *all* subgroup analyses are reported to diminish selection bias, (3) results are reported with estimated effect size and confidence intervals in each subgroup, (4) tests of interaction or multivariate risk score are performed, as appropriate, and others (at least until Bayesian approaches[436] are adopted and validated). Cooperative discussion and collaboration will be required to advance the field, and while agreement will be difficult, the current approaches are insufficient for statisticians to determine either appropriate subgroup-specific sample sizes or evidence of HTE.

12.3 Planning and evidence development

In any product development and any clinical research program, planning for subgroup analyses is important. Early in a clinical development program, when less is known about the product, conservative eligibility criteria (from a safety standpoint) are appropriate (see Section 13.3 "Eligibility criteria") in order to decrease the possibilities of harm. Nevertheless, when there is evidence of subgroup differences (or concerns that inclusion of a subgroup may be at increased risk), as may emerge during product development, observational data, other data sources, and other study designs may be appropriate to consider. Adaptive study designs should be investigated, allowing different elements to be considered (e.g., dose selection by subgroup, comorbidities, adolescent participants, the elderly, etc.). Such an approach safeguards participant safety and allows stratified benefit-risk assessments.

[435] These questions will also be determined based on the objective of the trial. For trials regulated by health regulatory authorities, often sponsors are required to pre-specific subgroups of interest.

[436] Note that some guidance already exists on this point. See "Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products," September 2019. "e.g. "the use of hierarchical models or other approaches that automatically downweight borrowing in the presence of heterogeneity." (p. 7, l ine 280). Available at Docket ID:FDA-2019-D-3679. https://www.fda.gov/media/130897/download [Accessed 2 July 2020.]

Some situations require inclusion of specific populations from early on in product development. There are situations where a disease is known to be more prevalent in a given subpopulation that is underrepresented in clinical trials. Clinical trials of treatment for sickle cell disease (SSD), for instance, more prevalent in Black individuals, require specific recruitment plans that may involve outreach to those communities and/or centers of excellence in SSD treatment, etc. Or there may be prior studies in one disease with a product of the same drug class or biological target that lead one reasonably to anticipate a different response in a particular subgroup; in that case, early trial design should incorporate that knowledge. This latter situation is more common in post-market research when more is known about heterogeneity of response, and recruitment of specific subpopulations may be appropriate.

12.4 Real World Data (RWD), Real World Evidence (RWE), and observational data

Attention to the magnitude of HTE depends upon the goals of the estimate: the results of analyses that would permit a regulatory agency to determine whether to approve a product for a general patient profile will differ from a treating physician who must decide whether to prescribe a product for an individual patient sitting on the examining table or for the patient deciding whether to take the treatment prescribed. Understanding HTE is limited by study sample size in clinical trials, a limitation that can be overcome by utilization of observational data. Observational data utilize data sources such as electronic health records (EHR), national and trans-national population registries, insurance claims, pharmacy data, and patient-reported data that are less limited in number but must be "fit-for-purpose."[437, 438] Further, these data sources, if derived from representative populations, will reflect the diversity of the population that has access to the treatment, including subgroups of interest (e.g., sex, age, race, ethnicity, comorbidities, etc.). The large sample size will also increase power and can be used to adjust for multiplicity issues. Observational data can both inform HTE and subgroup differences and satisfy required post-approval study requirements but are the representation of, and any systematic bias in, the populations of interest in the data sources. Insurance and payer claims

[437] Daniel G, Silcox C, Bryan J et al. White paper: characterizing RWD quality and relevancy for regulatory purposes. Available at: https://healthpolicy.duke.edu/sites/default/files/atoms/files/characterizing_rwd.pdf. [Accessed 22 June 2020].
[438] Girman CJ, Ritchey ME, Zhou W, Dreyer NA. Considerations in characterizing real-world data relevance and quality for regulatory purposes: A commentary. Pharmacoepidemiology and drug safety. 2019 Apr;28(4):439.

data, for example, might underrepresent economically-disadvantaged and marginalized populations. Analysis of claims data, including the economically-resourced populations--regardless of race and ethnicity status—may lead to conclusions that are not generalizable.

Another major concern with observational data is bias, a challenge that can be overcome, at least in part, by registration of the planned analysis and by randomization. Registration of the research in a public repository in advance of performing any statistical comparisons mitigates against selective reporting of trials (publication bias) and provides transparency to pre-specified, detailed analyses, limiting the number of covert protocol modifications. Prospective randomization has the benefit of balancing both known and unknown characteristics of comparison groups as well as investigator bias and other known problems. Prospective randomization requires development of patient cohorts and then the collection of trial data from observational "real world" endpoints, most commonly from the electronic medical records, and is rarely applicable for early-phase trials. Of course, even randomization will not account for all concerns with RWD (e.g., lack of high quality data collection, missing data, different endpoint definitions/criteria, and population heterogeneity) or disambiguate variables (or variables and an outcome) that are related to one another (e.g., renal function and age) but might nevertheless be useful in developing evidence to support the approval of new indications for an approved product. Ideally, during product development, real world data of outcome measures would be collected during randomized clinical trials to assess how faithfully they correlate with the measured outcome. Knowing how well some data element correlates with outcome will render post-approval RWE easier to develop and analyze.

12.5 Recommendations

RECOMMENDATIONS

POLICY

- Base sample size for subgroups on disease-specific epidemiological data.
- Require standard results reporting:
    - Methods and statistical analysis are adequately described
    - *All* subgroup analyses that have been performed must be reported
    - Results are reported with estimated effect size and confidence intervals in each subgroup
    - Tests of interaction (e.g., multivariate risk scores) are performed, as appropriate
- In addition to prospective interventional trials, require registration of observational studies.
- Evaluate database studies for representativeness of the patient population if used for observational trials.
- Increase number of post-market observational studies that analyze heterogeneity of treatment effect in different subgroups. Require post-market studies when evidence suggests important differences.

FOR FURTHER RESEARCH

- Validate the use of real world data (e.g., electronic medical records, patient reported outcomes, health insurance claims) that could serve as surrogates for, or outcomes of, treatment effect. Optimally, the correlation of real world data to outcome would be explored and validated during product development. If validated, then real world data using data sources that adequately reflect the diversity of the population could be used to enable post-trial observational trials that inform heterogeneity of treatment effect and safety parameters across subgroups.
- Develop methods to efficiently estimate treatment effects within subgroups:
    - Establish industry-wide shrinkage estimators

- Further develop Bayesian hierarchical model
  - Standardize considerations for setting statistical parameters (e.g., borrowing)
  - Standardize reporting of Bayesian models
- Develop innovative approaches

Part E – Study Design, Conduct, and Implementation

As noted in Parts A-D, lack of diversity in clinical research is not a new phenomenon or observation; many studies have investigated why it has been considered an intractable problem. In Chapter 13 "Study Protocol and Conduct," we draw from many sources to identify barriers and present opportunities to improve study design, logistics, and conduct. In the sections that follow, we include recommendations for **planning for inclusion** of diverse populations throughout the **product development and lifecycle** (Section 13.1), ensuring that various **study designs** (Section 13.2) accommodate diverse populations, broadening **eligibility criteria** (Section 13.3) to allow for greater inclusion of underrepresented populations, adapting a rigorous **feasibility assessment** (Section 13.4) and informing the site selection processes, developing effective strategies for **study conduct**, **recruiting and retaining** (Section 13.5) a diverse participant pool, including developing a **recruitment strategy document** (Section 13.5.1), as well as considerations on the topic of **payment** (Section 13.6). Note that while this chapter is not meant to be a complete review of all barriers, it is intended to inspire comprehensive thinking and consideration for those planning and conducting clinical research. In the sections that follow, we present a number of practical interventions. Some of these are easily implemented. Others require longer-term commitment and will vary depending on the product development phase, the particular study protocol, and the resources available to the sponsor, investigator, or study site.

In Chapter 14 "The Role and Responsibility of the IRB/REC in Inclusion and Equity," we describe **role and responsibilities of IRBs/RECs** in conducting ethical review and oversight.

We have reserved Chapter 15 "Special Populations" for future work and intend to develop content to stimulate understanding, advance preparedness, and facilitate the inclusion of special populations in research. The chapter will include guidance, points to consider, and adaptable tools.

13. Study Protocol and Conduct

13.1 Product development and lifecycle

KEY SUMMARY

- Diversity and inclusion are fundamental considerations not only of each clinical trial for a product but also across the larger clinical development pathway for that product, from pre-clinical work through market approval and post-approval research and pharmacovigilance.
- Generally, no single clinical trial will suffice to determine safety or efficacy in subpopulations, but each clinical trial contributes to and advances knowledge.
- Proactive planning and conscientious execution are required to prioritize diverse inclusion appropriately along a product's clinical development, based on the disease area, pre-clinical and evolving clinical data, and an understanding of safety, efficacy, and heterogeneity of treatment response.
- Understanding subgroup differences may be uniquely challenging for products developed for and tested in small populations (e.g., products for rare and ultra-rare diseases, products for neonatal conditions, etc.); developing appropriate structures and analyses pipelines can help ensure inclusivity and diverse representation, regardless of prevalence or disease subtype.

As discussed in Section 2.4 "Research and the utility of subgroups," questions about variability in subgroup response to treatment are generally not answered by any one clinical trial but should be considered along the timeline of product development and post-marketing data collection and analysis. Eligibility requirements for first-in-human (phase 1) trials, where variability in response may be high—since only pre-clinical data are available and little is known about safety and efficacy—are necessarily conservative. Enrolling those with multiple comorbidities, for example, may not only increase the risk to participants, but may confound any opportunity to understand the risks and benefits of the intervention itself. Similarly, for ethical reasons, additional safeguards should protect enrollment of vulnerable populations. The same logic (i.e., minimizing risk), however, does not apply to inclusion with regard to ethnic and

racial minority populations of a phase 3 registration trial; that phase 3 trial should include the range of populations for which the product is intended. Similarly, the populations of a post-approval comparative effectiveness trial comparing two products, the profiles of which have been known for some time, should reflect the as-treated population insofar as possible. Latitude in eligibility—and therefore the diversity of inclusion—is a function of what is known about the product or product class, the biology of the disease and the population with the condition, and several other factors including availability of alternative treatments. Planning for inclusion of diverse participants and underserved populations throughout the product clinical development and through all phases of its lifecycle is necessary, to the extent possible, to understand heterogeneity of treatment effect – including differences in safety and efficacy – regardless of the disease being studied or the rarity of the subgroup. To ensure diversity of study populations throughout the product clinical development, one company, for example, develops both an asset demographic plan, focused to the molecule's overall clinical development lifecycle as well as a trial specific demographic plan that is focused to the particular trial. (For detailed information refer to "Case Study: Focusing on Global Clinical Diversity as a Priority Point" in *Toolkit*.)

Many products are intended for and can only be studied in small populations; considerations of subgroup differences and heterogeneity of treatment effect are secondary and may not be possible at all. Products to treat rare and ultra-rare diseases, (e.g., treating inborn errors of metabolism, rare genetic subtypes of cancer, diseases that affect neonates) for instance, can only be tested in that rare population. It is important to validate safety and efficacy of a product that addresses an unmet clinical need (and similar exigencies) as expeditiously as possible. Demographic and non-demographic data should nevertheless continue to be collected to allow for later analysis at a time when sufficient numbers of treated patients have been collected. Collaboration across stakeholders involved in any part of the clinical research lifecycle to form a registry with the goal of permitting robust data collection is a worthwhile consideration.

RECOMMENDATIONS

- Proactively plan to track and analyze participation of diverse populations throughout the product lifecycle, at all phases of development, in different clinical trial designs, and/or in clinical research program, including:
    - Pre-clinical development (e.g., What is known about the epidemiology and pathophysiology of the disease? Were juvenile animals and animals of both sexes studied? What is known about the pharmacodynamics and pharmacokinetics of the product, the absorption, distribution, metabolism, and excretion of the product? Are these findings of relevance to known variability observed in human subpopulations? etc.)
    - Clinical development (e.g., Is this a first-in-human experiment? What is the intended population of the product? What is known about this product or product class in prior trials or data? Are there any data to suggest differences in the intended population? etc.)
    - Genomic correlations (e.g., What is known about the genetics or genomics of the disease, of variation across populations, of the drug metabolic pathways? etc.)
    - Post-approval research (e.g., Are there data to suggest differences in safety or efficacy in subpopulations? How can or should post-approval data collection inform an analysis of heterogeneity of effect, if any? Does safety reporting or pharmacovigilance efforts reveal subgroup differences? etc.)
- Collect and record data of the demographic and non-demographic variables of study populations in trials using uniform data standards in order to render data interoperable (see Chapter 11 "Data Variables and Collection").
- Review comprehensive data across all trials (and other data sources) for subgroup differences and heterogeneity of treatment effect.
- Over the course of the product development lifecycle, share data and associated metadata in a machine-readable format by sponsors and/or investigators, as early as possible, to permit broad analyses by subgroup and drug class (see Chapter 12 "Approach to Data Analysis"). Such analyses could be performed by academia or health regulatory authorities, or even innovator companies if sufficient data were available.

13.2 Study question and design

KEY SUMMARY

- In advance of a trial, the study question and study design should first address the diversity of the population and potential subgroup differences for which the product is intended (e.g., ancestry, comorbidities).
- Involvement and partnership of patients, their advocates, and communities are important for the development of the study question to ensure its relevance to the population of intended users of the treatment (see Chapter 8 "Participant and Community Engagement").
- Participation of appropriate and diverse populations during study design, in planning the conduct of the study, and in the development of recruitment and retention strategies may increase the likelihood that the intended population will agree and be able to participate.

Research begins with a study question informed by background, a landscape analysis of previous work regarding the product and product class, the intervention, population with the disease or condition, and the focus of the research. As reviewed in Chapter 2 "The Case for Diversity in Clinical Research," clinical trials should be designed to address the population intended to take or use the treatment. However, data indicate that minorities, adolescents, young adults and older populations are often not adequately represented: in the ten-year time frame from 2004-2014, over half of coronary artery disease trials failed to include *any* patients over the age of 75 years despite the greater prevalence of coronary artery disease in the elderly and the fact that approximately 15% of the U.S. population was elderly at the time of report.[439] Similarly, according to the American Society for Clinical Oncology (ASCO), in pivotal cancer immunotherapy trials, only 0–4% of study participants were Black or African-American and 4% were Hispanic/Latino despite the prevalence of disease being higher in those groups than in

[439] FDA hearing highlights research gaps for women, minorities and the elderly. April 2014. Online: https://news.heart.org/fda-hearing-highlights-research-gaps-for-women-minorities-and-the-elderly/ [Accessed 22 June 2020]

White populations.[440] In data collected by Syneos Health, Hispanic/Latino individuals represent nearly 18% of the population, yet fewer than 5% of the Hispanic/Latino population participate in clinical trials, and only about 1% of cancer clinical trial participants.[441] For some cancer patients, participation in clinical trials may represent the only opportunity to access novel therapies. Exclusion of any demographic subpopulation (e.g., "non-English speaking") or vulnerable populations from research reduces access to potentially life-saving therapies as well as the opportunity to contribute to the public good, whether exclusion was due to lack of awareness, access, restrictive eligibility criteria, burden of participation, or because the study was not designed with underrepresented groups in mind.

As mentioned in Chapter 8 "Participant and Community Engagement," engagement with patients, participants, their advocates and communities, and with direct health care providers can inform the research question and help ensure that the outcomes or endpoints of the research will be of relevance and interest to those individuals and communities. Participant and community engagement can prospectively identify unnecessary restrictions on eligibility criteria, confirm research tests and data collection methods are achievable, and ensure the intended populations can be reached with planned study recruitment materials. Whether the connection is established by the researcher, the clinical research site, the institution, or by the sponsor or manufacturer is less important than the authenticity and persistence of the partnership.

As mentioned in Section 13.1 "Product development and lifecycle," sponsors and investigators should consider the condition or disease, the affected population, and information on the product itself (e.g., pre-clinical data, ADME,[442] prior clinical trial and observational data, etc.) in

[440] Nazha B, Mishra M, Pentz R, Owonikoko TK. Enrollment of Racial Minorities in Clinical Trials: Old Problem Assumes New Urgency in the Age of Immunotherapy. American Society of Clinical Oncology Educational Book. 2019: 39, 3-10.
[441] Dornsife D, Richie N, Monroe S, Sandoval F. How to boost racial, ethnic and gender diversity in clinical research. Syneos Health. 2019. Online: https://www.syneoshealth.com/sites/default/files/careers/Diversity_in_Clinical_Research_FINAL.pdf [Accessed 22 June 2020]
[442] ADME is an abbreviation used in pharmacology and pharmacokinetics to reference the **a**bsorption, **d**istribution, **m**etabolism and **e**xcretion of a compound within an organism.

developing a study design that is as "feasible, efficient, and cost effective"[443] as possible. In this context, questions of subgroup differences should be addressed in advance and planned: trial design, statistical considerations, feasibility assessments, recruitment, tracking, data collection, and analysis must be engineered to achieve that planned purpose. Thoughtful inclusion of underrepresented groups in designing the study may increase the likelihood that the intended population will be able and willing to participate in the study (see "Introduction to Logic Models," "Logic Model: Study Design," and "Study Design KPIs" in *Toolkit*).[444] Intentional planning of a study also enables trial sponsors, investigators, and study teams to budget sufficient time, money, and other resources to recruit and retain diverse participant pools, as well as anticipate scheduling and other needs with flexibility.

Sponsors and investigators can consider not only traditional but innovative trial designs to optimize enrollment, engagement, and diversity, to the extent possible.[445] For example, pragmatic studies tend to increase the diversity of the study population as a result of more permissive eligibility criteria and, often, more modest risk, simpler (or waived) consent procedures, and participant familiarity with the study intervention. Minimizing research procedures and participant burden, whether by reducing study visits, bringing the study closer to the participants (e.g., offering study visits at home, at a local community health center, or, as privacy allows, the workplace), and/or considering additional time commitments related to the study, will improve overall participation and diversity. Adaptive clinical trials and platform

Figure 27: Case example: Apoyo on Cariño

> Apoyo con Cariño (Support with Caring), a randomized clinical trial studying palliative care for LatinX adults with advanced cancer, demonstrated high retention rates attributed to engaging community health centers and safety-net healthcare institutions, incentivizing bilingual rural health workers to conduct research activities, and visiting patients in their home in and outside of normal working hours.

[443] Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing Clinical Research. 2007. 3rd edition. Philadelphia, PA.
[444] Huang GD, Bull J, McKee KJ, Mahon E, Harper B, Roberts JN. Clinical trials recruitment planning: a proposed framework from the Clinical Trials Transformation Initiative. Contemporary clinical trials. 2018 Mar 1;66:74-9.
[445] Metzger, D.A. White Paper: Is Patient Centricity Truly at the core of Clinical Trials? KNect 365 Life Sciences. Available at: https://knect365.com/clinical-trials-innovation/article/8d4ad6db-0dde-4ddf-8def-5b569c1f4c91/whitepaper-is-patient-centricity-truly-at-the-core-of-clinical-trials. [Accessed 22 June 2020].

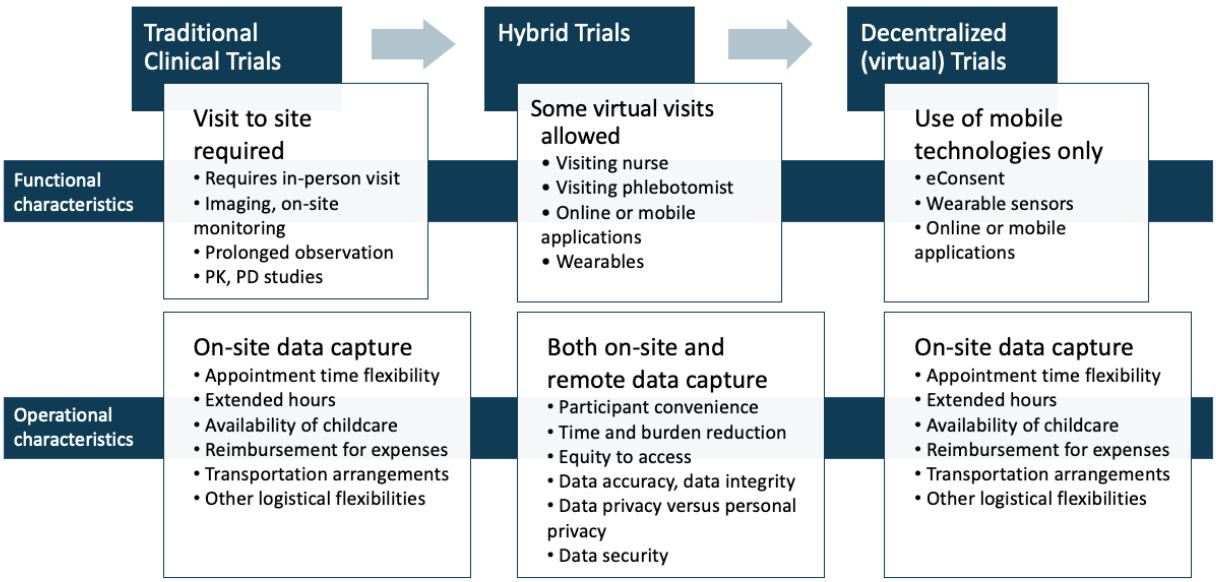
trials may increase enrollment in clinical trials and hasten data generation during product development prior to approval.

Special provisions may be required to enroll and retain participants in trials of rare diseases with geographically dispersed populations.[446,447] For example, moving the clinical research setting from a hospital or clinic to the home or to community health centers may help accommodate those individuals unable to travel for reasons related to mobility, expense, time, or other.[448] Necessary support and planning need to be in place for the study to be performed correctly. For example, decentralized trials (see Figure 27, *Apoyo con Cariño*[449]), where there is no central trial facility and research is conducted entirely or partially remotely, can help increase the pool of potential participants as well as improve retention and, therefore, successful trial completion. Decentralized clinical trials often use mobile technologies and/or applications, not only in high-income settings for convenience and cost savings but also in low- and middle-income countries (LMICs) where smart phone access is steadily increasing.[450] The thoughtful planning and deployment of mobile technologies offer additional advantages, including electronic consent, integrated data sensors, real-time opportunities for patient-reported outcomes and other data to be captured electronically, and tele-visits and videoconferencing (see "Case Study: Data-driven Diversity Assessments at a Medical Device Company" in *Toolkit*). For hard-to-reach populations (e.g., rural settings, immigrant or nomadic populations), home-based health care, mobile research units, and mobile applications aid in data collection, reporting, and ease of participation. Of course to be successful, as with any trial, a decentralized trial—or a trial that adopts some elements of mobile technologies even if not entirely virtual—must be done with the proper supportive operational infrastructure (e.g.,

[446] Winter SS, Page-Reeves JM, Page KA, Haozous E, Solares A, Nicole Cordova C, Larson RS. Inclusion of special populations in clinical research: important considerations and guidelines. *J Clin Transl Res*. 2018 Apr 7;4(1):56-69.
[447] Gelinas L, Crawford B, Kelman A, Bierer BE. Relocation of study participants for rare and ultra-rare disease trials: Ethics and operations. Contemporary clinical trials. 2019 Sep 1;84:105812.
[448] Kurt A, Semler L, Jacoby JL, Johnson MB, Careyva BA, Stello B, Friel T, Knouse MC, Kincaid H, Smulian JC. Racial differences among factors associated with participation in clinical research trials. Journal of racial and ethnic health disparities. 2017 Oct 1;4(5):827-36.
[449] Fischer SM, Kline DM, Min SJ, Okuyama S, Fink RM. Apoyo con Carino: strategies to promote recruiting, enrolling, and retaining Latinos in a cancer clinical trial. Journal of the National Comprehensive Cancer Network. 2017 Nov 1;15(11):1392-9.
[450] Landert K, Steel A. Direct-To-Patient Remote Research [Internet]. ClinPal. Available from: https://www.clinpal.com/wp-content/uploads/2018/05/White-Paper_Direct_to_Patient-Remote-Research_2.pdf [Accessed 22 June 2020].

off-site clinics, continuous supply-chain management, communications, or even the availability of consistent electricity, etc.; see Figure 28 "Functional and operational characteristics of traditional and innovative clinical trials").

Figure 28: Functional and operational characteristics of traditional and innovative clinical trials



In traditional clinical trials, "on-site data capture" provides some of the associated operational characteristics to increase diverse inclusion. The boxes for hybrid trials (both on site and virtual) and decentralized (virtual) trials identify characteristics of these approaches.

RECOMMENDATIONS

- Engage patients, participants, advocates, and communities prior to and throughout the study design to review research tests, data collection methods and outcome measures and throughout the drug development process (see Chapter 8 "Participant and Community Engagement"), in order to:
    - Ensure relevance of the study question and primary and secondary outcome measures.
    - Optimize study design.
    - Minimize study burden, including study research procedures, logistical arrangements and flexibilities (appointment time scheduling, reimbursement, childcare, transportation, etc.; see Section 13.5 "Study conduct, recruitment and retention"), and duration while maintaining study and data integrity.
    - Determine if any additional modifications, simplifications, or explanations are required to facilitate enrollment, participation, and retention in the research.
- Review eligibility criteria in relation to the population that is intended to use or take the intervention, maximizing inclusivity, and document scientific rationale for any limitations to enrollment (e.g., exclusion criteria).
- Ensure the intended population can be reached with the planned study recruitment methods:
    - Incorporate health-literate communications (e.g., translations, plain language, etc.), including communications methods accessible to individuals with cognitive and sensory disabilities (e.g., audible readings of information, large type formats, video explanations) and communications specific to the relevant community (e.g., appropriate translations and word choice, representative pictures if included).
    - Conduct user testing of study documents (e.g., advertisements, instructions, informed consent documents) for comprehension to the prospective participant.
- Determine whether and which research procedures can be performed locally or virtually:
    - Validate any mobile technologies that will be used, not only for data integrity but also for acceptability to the study populations.
    - Consider privacy and with whom collected data will be shared.
    - Consider data validation, accuracy, security, etc.

13.3 Eligibility criteria

KEY SUMMARY

- Study design can influence eligibility criteria; adaptive trials, for example, can increase diversity through progressive modifications in eligibility consistent with data demonstrating safety.
- Study protocols should include a scientific or ethical justification for the exclusion of certain populations, and that justification should be reviewed by oversight committees (e.g., IRB/RECs, DMCs).
- Eligibility criteria should be objective.
- Eligibility criteria should be as broad as possible and as narrow as necessary. Narrow eligibility criteria create greater *similarity* among the participating individuals in a trial, limiting heterogeneity and optimizing consistency in results (internal consistency).[451] More permissive eligibility criteria create a more *diverse* participant population, potentially increasing heterogeneity of results but equally potentially revealing a differential effect on outcomes and increasing generalizability of results (external validity).
- When there is strong prior evidence of heterogeneity of treatment effect (suggested by pre-clinical data, knowledge of relevant metabolic pathways, prior information derived from drug class, etc.), eligibility criteria should be broad—or advertently broadened at an appropriate time—to include these different subgroups in the product development program.
- Study protocols should include a scientific or ethical justification for the exclusion of certain populations, and that justification should be reviewed by oversight committees (e.g., IRB/RECs, DMCs).

When designing clinical trials, there is a tension between balancing the desire to minimize heterogeneity ("noise"), which can mask a finding of the effect, and the desire to generate data that are generalizable to a broader patient population that is likely to be treated. Narrow eligibility criteria can result in (1) a homogeneous sample of subjects, limiting the variability in a study population, and (2) controlling for confounding factors, maximizing the probability of detecting a treatment effect if one

[451] As discussed later in this section, consistent results, however, do not necessarily result in rejecting the null hypothesis (i.e., demonstrating an "affect").

> exists. On the other hand, narrow eligibility criteria can diminish the understanding of the risk-benefit of the study treatment relevant to the patient population likely to take the drug if the drug is approved.
>
> *FDA. Public Workshop: Evaluating Inclusion and Exclusion Criteria*[452]

In any clinical trial, the findings of the study are a result of the analysis of the aggregate population enrolled in the trial and, of course, a function of study design. More *similarity* among the participating individuals in a trial limits heterogeneity and leads to more consistent results;[453] the more *diverse* a population, the greater the variability of the results. When there is strong prior evidence of heterogeneity of treatment effect or differences between subgroups, certain strategies should be employed to assess variation in treatment response including innovative statistical analysis (e.g., stratification, planned subgroup analysis; see Chapter 12 "Approach to Data Analysis") and novel study designs (e.g., adaptive clinical trials; see Section 13.2 "Study question and design").

The more that is known about the disease or treatment in advance of a trial, the more potential differences in response may be taken into account, thus informing study design and eligibility criteria. There are two types of differences in response to be considered: (1) differences in prognosis (e.g., older patients and those with comorbidities tend to have worse outcomes, even if a given treatment benefits them just as much as it benefits others) and (2) heterogeneity of treatment effects (e.g., patients who lack a certain enzyme may benefit less from a treatment than other patients, even if patients with and without the enzyme tend to have similar prognoses).

[452] U.S. Food and Drug Administration.. Public Workshop: Evaluating Inclusion and Exclusion Criteria. Workshop Report, July 2018. The National Press Club. Washington DC. April 16, 2018. Available at: https://www.fda.gov/media/134754/download. [Accessed 2 August 2020]

[453] Notably, however, consistent results do not necessarily imply that the null hypothesis will be rejected. It is possible that the "consistent result" will be a negative result (i.e., accepting the null hypothesis), wherein a subgroup as reflected in a more heterogeneous population may demonstrate a difference that can be further explored.

Figure 29: Example of predictive factors for metabolic differences

Sometimes, there are known predictive factors (e.g. CYP450 genes) of fast or slow metabolism that inform the pharmacodynamics and pharmacokinetics, how long the drug remains in system, and therefore the dosing required. Liver and kidney functions may sometimes be used as a surrogate if genetic testing is not available.

In advance of a therapeutic development program, knowledge of subgroup variability may be deduced by pre-clinical data, epidemiology of the disease or population, knowledge of relevant metabolic pathways, prior information derived from drug class, and other indicators. In the development of drugs, for instance, predictors of slow or fast metabolism (e.g., the CYP450 family of genes; see Figure 29) [454,455,456] will impact the rate of metabolism and therefore drug pharmacokinetics (PK) and pharmacodynamics (PD), drug-drug interactions, and potential efficacy and toxicity. Early PK/PD studies are advisable, genetic screening in advance of drug administration may be considered, and determinations of hepatic and renal function would be useful. If the drug has a narrow therapeutic window,[457] observing drug blood levels to minimize risks and ensure correct therapeutic levels for efficacy may be helpful. Often, however, differences with respect to the effect of the treatment between individuals and subgroups are unknown in advance of a trial and therefore cannot inform planned design and analyses. It is important to understand any heterogeneity of response to know whether and when the results are generalizable.

[454] Cytochrome p450 (CYP450) genes encode enzymes that are involved in the formation (synthesis) and breakdown (metabolism) of various molecules in cells, and for the purposes here, most notably in the metabolism of medications. There are over 60 genetic variations (polymorphisms) of the CYP450 gene, leading to either the rapid or slow metabolism of a medication. If a drug is slowly metabolized, the drug persists for longer and may require a decreased dose or prolonged interval of dosing. If the drug is rapidly metabolized, a higher (or more frequent) dose may be needed.

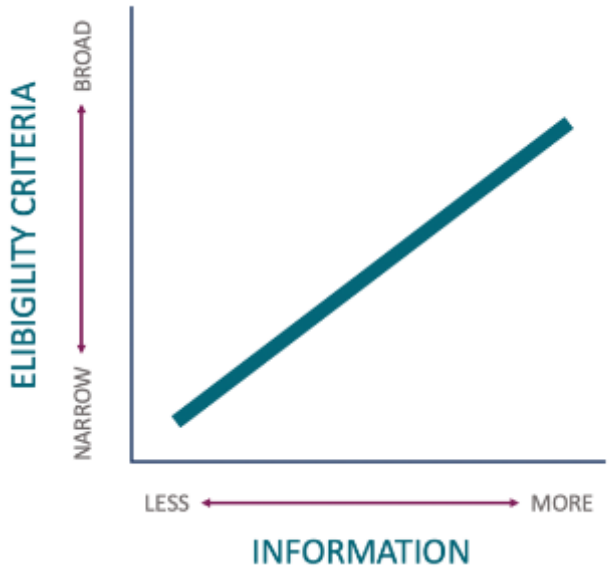
[455] See for instance, Indiana University Department of Medicine Clinical Pharmacology. Drug Interactions. Defining genetic influences on pharmacologic responses. https://drug-interactions.medicine.iu.edu/MainTable.aspx [Accessed 22 June 2020].

[456] University of Minnesota. Inhibitors, inducers and Substrates of Cytochrome P450 isozymes. See https://www.d.umn.edu/~jfitzake/Lectures/DMED/TAA/Q_A/CYP450InteractionTable.htm [Accessed 22 June 2020].

[457] The therapeutic window refers to the range of doses that produces a therapeutic response without causing significant adverse effects in individuals (i.e., the doses that provide efficacy without unacceptable toxicity.

Eligibility criteria serve the important function of minimizing harm to individuals involved in investigational interventions and other aspects of clinical research participation. Participants may be excluded from research for a variety of reasons, including contraindication or anticipation of an unacceptable risk of harm. This, while protective for some, may have the unwanted effect of limiting the inclusion of diverse study participants.[458] Eligibility criteria may also be selected to optimize the chance of demonstrating efficacy for a given condition, particularly during product development. Narrowing eligibility of the population may appear to enable a shorter, smaller, and less costly trial, and an earlier regulatory decision regarding safety and efficacy of the product.[459] At the same time, limiting eligibility criteria will decrease the number of individuals who meet inclusion and exclusion criteria and it will limit knowledge about the generalizability of the results (see Figure 30). Further, eligibility criteria are often simply "passed-down" from protocol to protocol under an investigator, institution, or sponsor without an evident clinical or scientific reason. Achieving the right balance between inclusion and exclusion, between homogeneity and heterogeneity, and between short- and long-term considerations of risk requires a planned and rational approach to the development of a study's eligibility criteria. Resolution of this tension requires deliberate consideration of

Figure 30: Theoretical visualization for broadening eligibility criteria



Theoretical visualization of the dynamic approach to broadening eligibility criteria as information (e.g., safety, efficacy) is gathered on an intervention over time (assuming information increases over time during clinical development). Of course, the line is not linear in practice.

[458] For example, commonly employed upper age restrictions on clinical trial participation may limit risk related to comorbid illness more often present in older populations, but it also limits information regarding study outcome in these older patients (with and without comorbid illness).
[459] If the result is "positive" in that it rejects the null hypothesis.

what is known and what remains unknown, based on pre-clinical and clinical data, and the employment of other safeguards to limit risk while permitting inclusion, when feasible.

Inclusion criteria of most trials generally allow participation of both men and women, unless, for instance, there is a biological reason for exclusion (e.g., trials of prostate or breast cancer[460] treatment, phase 1 trials of healthy males in order to eliminate any risks to women of child-bearing age). Similarly, eligibility criteria associated with race and ethnicity criteria are not usually specified.[461] It is common, however, to exclude individuals based on age (e.g., children, adolescents, the elderly), existing comorbidities polypharmacy, and pregnant or lactating women (see Section 13.3.1 "Case examples" below).[462] Notably, many clinical trials include cut-offs for age without justification.[463] The International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has encouraged greater inclusion of both older[464] and younger individuals, where physiologically feasible. Protocols often explain why a certain population is focused upon for enrollment, but rarely do protocols include a scientific or ethical justification for the exclusion of certain populations.[465, 466] While there may be safety or other reasons for these eligibility criteria—and restricting the eligible population may be particularly important before there is evidence of benefit of a treatment—those reasons, if they exist, are rarely explained or defended in study protocols. Except for very

[460] The FDA has recently called for inclusion of male patients with breast cancer in clinical trials. See U.S. FDA. FDA in Brief: FDA encourages inclusion of male patients in breast cancer clinical trials. August 26, 2019. See https://www.fda.gov/news-events/fda-brief/fda-brief-fda-encourages-inclusion-male-patients-breast-cancer-clinical-trials. [Accessed 22 June 2020].
[461] Underrepresentation in completed trials is likely due to barriers other than explicit inclusion or exclusion criteria.
[462] Women of child-bearing age often are asked to agree to using appropriate contraception during an interventional trial unless the effects on pregnancy and the developing fetus are known.
[463] Buttorff C, Rude T, Bauman M, Multiple Chronic Conditions in the United States, Rand Corporation, 2017, https://www.rand.org/pubs/tools/TL221.html. [Accessed 22 June 2020].
[464] ICH-E7 Studies in Support of Special Populations: Geriatrics, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073131.pdf. [Accessed 22 June 2020].
[465] Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. Journal of general internal medicine. 2011 Jul 1;26(7):783-90.
[466] Spong CY, Bianchi DW. Improving public health requires inclusion of underrepresented populations in research. Jama. 2018 Jan 23;319(4):337-8.
[467] Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. JNCI: Journal of the National Cancer Institute. 2019 Feb 19;111(3):245-55

obvious reasons (e.g., an individual must have the disease under study), it is equally important to explain why an otherwise appropriate population is excluded as one that is permitted to enroll.

Figure 31: Example of eligibility criteria limiting patient access to cancer trials

A systematic analysis of U.S.-based cancer patient enrollment found that clinical and/or structural barriers prevented over 55% of patients from participating in a trial. An appropriate trial for an individual by diagnosis and stage was simply not available where the patient was being treated, whether that was in an urban academic treatment center or a community-based care center. Additionally, another 21.5% of patients failed to meet eligibility criteria, mostly due to comorbid conditions with limited impact on the cancer outcome. Therefore, for oncology trials in the U.S., over 75% of patients were unable to enroll because of the study design or the research site location; they simply were never offered the opportunity to consider participating in a trial.

Eligibility criteria should be as inclusive as possible and consistent with what is known about the product's safety and efficacy at the particular phase of development, and any limitations in planned enrollment should be based on clinical, scientific, or other important reasons (see "Eligibility & Enrollment Log" and "Screen Failure Tracking Log" in *Toolkit*). As studies progress through development, bolstered by the collection of more information regarding safety and efficacy, study eligibility criteria can be broadened (see Figure 31).[468] Indeed, evaluating the population distribution for appropriate inclusion in completed studies can help inform future recruitment and retention strategies for underrepresented populations. Each eligibility criterion should be subject to explanation and justification; we recommend the eligibility criteria be reviewed by ethics and oversight committees (e.g., IRB/REC and Data Monitoring Committees [DMCs], respectively) to ensure that the choice of participant population is considered reasonable, appropriate, and as inclusive as possible. Diversity should be viewed in the totality of a clinical development program and studies conducted post-approval (e.g., comparative effectiveness studies) should address populations included in the

[468] Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. JNCI: Journal of the National Cancer Institute. 2019 Feb 19;111(3):245-55

product label, even—and most particularly—if they were not sufficiently included in the product development program.

Eligibility should be based on objective criteria and documented to maximize the pool of potential clinical trial participants. The next few pages include a number of examples of questionable or problematic eligibility criteria that serve to restrict the potential participant population unnecessarily or inappropriately. A fuller understanding of these examples—and potential strategies to rectify the problems—will help to raise awareness and, hopefully, change the inclusivity of eligibility criteria going forward.

13.3.1 Case examples

13.3.1.1 Serum creatinine as a proxy for kidney function

There is evidence that eligibility criteria can be inappropriately restrictive, leading to study populations that are not representative of the intended patient population. For example, eligibility criteria based on serum creatinine (sCr) alone as a proxy for kidney function (GFR) may inappropriately underestimate GFR in some Black patients.[469] Research conducted in the U.S. and Europe found Black individuals to have a higher estimated GFR based on sCr compared to White individuals secondary to factors other than the actual GFR (likely because of increased generation of creatinine from muscle and impact of diet).[470,471,472,473] Of note, the same

[469] Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Annals of internal medicine. 1999 Mar 16;130(6):461-70.

[470] Jones CY, Jones CA, Wilson IB, Knox TA, Levey AS, Spiegelman D, Gorbach SL, Van Lente F, Stevens LA. Cystatin C and creatinine in an HIV cohort: the nutrition for healthy living study. American Journal of Kidney Diseases. 2008 Jun 1;51(6):914-24.

[471] Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, Hamm LL, Lewis JB, Mauer M, Navis GJ, Steffes MW. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. American Journal of Kidney Diseases. 2010 Sep 1;56(3):486-95.

[472] Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, Heilberg IP. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clinical Journal of the American Society of Nephrology. 2008 Mar 1;3(2):348-54.

[473] But note that later research suggested that some equations (e.g. CKD-CPI) may not be accurate for European Black individuals. Flamant M, Vidal-Petiot E, Metzger M, Haymann JP, Letavernier E, Delatour V, Karras A, Thervet E, Boffa JJ, Houillier P, Stengel B. Performance of GFR estimating equations in African Europeans: basis for a lower race-ethnicity factor than in African Americans. American Journal of Kidney Diseases. 2013 Jul 1;62(1):182-4.

difference did not apply accurately to South African Black persons.[474] Despite evidence of the inadequacy of sCr to estimate GFR in some Black patients, eligibility criteria do not provide for this benign variant.[475] Suggestions to incorporate more objective measures such as height and weight for determining eGFR equations have been proffered,[476] as have adjustments for other known variations of laboratory values based on known differences in race and ethnicity. These corrections should apply only as they serve to increase representation in clinical trials, not to increase or exacerbate health inequities in clinical care.[477]

13.3.1.2 Benign variants of normal laboratory values

Eligibility criteria based on "normal" reference laboratory values should be adjusted if those normal values differ by subpopulations, such as race and ethnicity, age, sex and gender. It is well known, for instance, that the average height and weight differs between men and women, although an individual woman may be taller or heavier than an individual man. Despite the vast number of routine laboratory tests performed daily, however, reference intervals for routine laboratory tests based on race, ethnicity, and geography, and often sex, age, and body mass index are not generally available.[478] A few exceptions exist that demonstrate that such an approach is possible: pediatric studies are all qualified for the age of the child as it is well known that laboratory values (e.g., hemoglobin) vary by age. In the adult population, exceptions are often made for Gilbert's Syndrome, a known genetic condition in which the liver does not properly metabolize bilirubin, resulting in a higher unconjugated bilirubin than normal and mild jaundice. Eligibility criteria often permit higher levels of bilirubin in cases of known Gilbert's

[474] Stevens LA, Claybon MA, Schmid CH, Chen J, Horio M, Imai E, Nelson RG, Van Deventer M, Wang HY, Zuo L, Zhang YL. Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating the glomerular filtration rate in multiple ethnicities. Kidney international. 2011 Mar 1;79(5):555-62.

[475] Systematic changes must be considered carefully, however, and from many perspectives. A correction factor for GFR introduced for Blacks (and younger aged patients) had unwanted consequences in the U.S., impacting placement on transplant lists and leading to inequities in care. See Avi-Yonah S. Are kidney tests misdiagnosing African Americans? 2019, August 8. The American Prospect, Available at: https://prospect.org/health/kidney-tests-misdiagnosing-african-americans/. [Accessed 22 June 2020].

[476] Eneanya ND, Yang W, Reese PP. Reconsidering the consequences of using race to estimate kidney function. Jama. 2019 Jul 9;322(2):113-4.

[477] Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight—reconsidering the use of race correction in clinical algorithms. New England J Medicine. June 20, 2020. DOI: 10.1056/NEJMms2004740
Available at: https://www.nejm.org/doi/full/10.1056/NEJMms2004740. [Accessed 2 August 2020]

[478] Lim E, Miyamura J, Chen JJ. Racial/ethnic-specific reference intervals for common laboratory tests: a comparison among Asians, Blacks, Hispanics, and White. Hawai'i Journal of Medicine & Public Health. 2015 Sep;74(9):302.

disease. Eligibility criteria in documented cases of benign variants should be modified, thereby permitting a larger proportion of individuals to enroll.

One example demonstrates that the lack of adjusting laboratory values discriminates against certain populations. It is known that roughly 8% of Black individuals have a condition known as benign ethnic neutropenia, in which the neutrophil[479] count is low despite normal immune function.[480] In one meta-analysis of 401 interventional prostate cancer clinical trials, over 25% of studies excluded patients based on sCR alone, and 40% of studies excluded patients based on neutrophil count alone, criteria that disproportionately affected whether Black patients were eligible to participate.[481] Eligibility criteria did not make provisions for benign ethnic or racial differences.[482]

13.3.1.3 Investigator discretion

Overly vague criteria for inclusion and exclusion give rise to other shortcomings. The absence of objective criteria (e.g., chronic kidney disease) and method of ascertainment (estimated GFR <59 mL/min), risks non-systematic exclusion and unwanted bias in participant selection. A common example is the use of "investigators discretion" or "clinician judgement" as a criterion. By this criterion, if for some (or any) reason, an investigator does not believe that a potential participant would be a viable candidate to enroll, the investigator can decline to offer the trial for consideration. The reasons for exclusion, why an investigator might decide not to offer enrollment, are generally not documented, and thus the criterion itself increases the potential for selection bias.[483] Some excluded patients may simply seem frail, appear unable to comply

[479] A neutrophil is one type of circulating white blood cell that is important in the immune response and the fight against infection.
[480] Hsieh MM, Everhart JE, Byrd-Holt DD, Tisdale JF, Rodgers GP. Prevalence of neutropenia in the U.S. population: age, sex, smoking status, and ethnic differences. Annals of internal medicine. 2007 Apr 3;146(7):486-92.
[481] Vastola ME, Yang DD, Muralidhar V, Mahal BA, Lathan CS, McGregor BA, Nguyen PL. Laboratory Eligibility Criteria as Potential Barriers to Participation by Black Men in Prostate Cancer Clinical Trials. JAMA oncology. 2018 Mar 1;4(3):413-4.
[482] Rarely, deviations from approved eligibility criteria may be requested by the sponsor in order to accommodate a potential participant with known benign ethnic neutropenia, but that is a very uncommon, and labor-intensive solution.
[483] There are, of course, many other drivers of selection bias in a clinical trial, including the fact that some potential participants are never considered for enrollment. Eliminating investigator bias will decrease but not eliminate selection bias.

with the schedule of visits or challenged by the research procedures, overwhelmed by a new diagnosis, or considered unlikely to adhere to the specified requirements of the trial. Participant selection may be impacted by implicit bias.[484,485,486] Documentation and unbiased, external review of the reasons for exercising investigator discretion will help to diminish any arbitrariness in its use. The use of objective criteria and operationalized descriptions of how these are determined mitigates such shortcomings in screening and recruitment.

13.3.1.4 Ineligible individuals

The reasons that potential participants are determined to be ineligible to enroll in a research study are, generally, not systematically collected or analyzed unless screening parameters are part of the research study itself.[487] Many potential participants are deemed ineligible based on routine tests, and therefore never offered enrollment. Understandably, capturing information on all potential participants for eligibility is burdensome and inefficient. However, data on the reasons for ineligibility would enable investigators to determine whether criteria need to be modified to be more objective or inclusive. More importantly, failure rates based on normally collected clinical data would permit better understanding of the eligibility criteria that consistently limit inclusion. Unfortunately, even when ineligibility is documented, verification is difficult[488] and the data often not analyzed.

[484] Cooper LA, Roter DL, Carson KA, Beach MC, Sabin JA, Greenwald AG, Inui TS. The associations of clinicians' implicit attitudes about race with medical visit communication and patient ratings of interpersonal care. American journal of public health. 2012 May;102(5):979-87.
[485] Krumholz HM, Gross CP, Peterson ED, Barron HV, Radford MJ, Parsons LS, Every NR. Is there evidence of implicit exclusion criteria for elderly subjects in randomized trials? Evidence from the GUSTO-1 study. American heart journal. 2003 Nov 1;146(5):839-47.
[486] Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. Archives of internal medicine. 2002 Aug 12;162(15).
[487] The example cited here occurs when the criteria for protocol entry are determined by routine clinical data and are not part of the protocol itself. If the protocol specifies certain "screening" values or procedures after a signed informed consent and enrollment, those results are captured.
[488] Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomized trials. Journal of clinical epidemiology. 2010 Aug 1;63(8):e1-37.

RECOMMENDATIONS – ELIGIBILITY CRITERIA

POLICY

- Develop and adopt, where permissible, global standards for race and ethnicity. In addition to relevance for data collection and analysis (see Part D "Data Standards and Analysis"), these standards are necessary to establish study variation in outcome by race and ethnicity.
- Require explanations in the protocol for scientific rationale and justification on each eligibility criterion (inclusion and exclusion); where necessary, the rationale should be examined prior to approval, during all scientific and ethical reviews, and by the regulatory authorities and ethics committees;
    - For instance, if exclusion criteria include an age limitation, a rationale and justification for the proposed age range should be included in the protocol as well as the scientific or other reasons for not including other ages in the population.
- Devise eligibility criteria with reference intervals for routine laboratory tests based on race, ethnicity, and geography, as well as for sex, age, and body mass index. Where appropriate reference intervals are unknown, future research is encouraged.[489]
- Develop a global, searchable, and accessible repository of normal values (e.g., BMI, HgA1c, blood pressure, hemoglobin, white blood cell count, creatinine clearance, etc.) for different subgroups. Such a repository would serve the general purpose of not excluding subgroups unnecessarily or inappropriately.

OPERATIONAL

- Consider anew for each trial inclusion and exclusion criteria rather than simply adopting the criteria from prior trials.
- Inclusion and exclusion criteria should rely on:
    - objective determinations, where possible;
    - methods to determine eligibility which are, insofar as possible, routine and not subject to investigator or participant bias; and

[489] Lim E, Miyamura J, Chen JJ. Racial/ethnic-specific reference intervals for common laboratory tests: a comparison among Asians, Blacks, Hispanics, and White. Hawai'i Journal of Medicine & Public Health. 2015 Sep;74(9):302.

    - relevant laboratory values for the individual being studied – in other words, variations in laboratory values by age, race, or ethnicity need to be established and incorporated.
- Develop a plan for widening inclusion criteria, based on an early understanding of drug metabolism and response through:
    - PK/PD studies;
    - Impact of hepatic and renal dysfunction; and
    - genetic screening, as appropriate.
- Report all inclusion and exclusion criteria transparently in clinical trial documents and registration materials, to IRB/RECs, and in publications.
- Require all eligibility criteria to be listed in public registration repositories.
- Ensure demographic questions are included in all standard case report forms and in training materials (see "Data Variables Tool" in *Toolkit*).
    - Some regions disallow collection of specific data such as race or ethnicity. Sponsors will need to determine whether the prohibition is law, regulation, guidance, or custom, and require data collection if legal.
- Ask patients to self-identify and do not allow sites, investigators and their study staff to record personal assumptions (e.g., Black, Hispanic/Latino, etc.).
    - Specific training on methods for data collection should be provided by the sponsor and/or institution and site.
- Avoid inclusion and exclusion of participants based on investigator discretion and, to the extent the subjective determinations are necessary, the basis for the determination should be documented. Such documentation will then need to be reviewed by the principal investigator or designee, the sponsor, or the cognizant IRB/REC at least annually at continuing review, or more frequently if requested or required.
    - Objective measures must be used to document the basis of investigator decision, if possible.
    - Explanations such as "unlikely to complete trial procedures" and "likely adherence problem" need to be further clarified and subject to scrutiny.
    - Screen failure data should be systematically collected and analyzed.

    - Additional methods for systematizing screening procedures[490]—and recording reasons for screen failure[491]—should be evaluated.
- Provide clinical or scientific evidence to support inclusion/exclusion criteria whenever possible and collect the reasons that eligible, potential participants decline to enroll and periodically analyze these data (by the sponsor) to evaluate for actionable solutions.
- Prior to study initiation, offer translations or determine the necessary language requirements for potential participants. Eligibility criteria that require English language (or other native language) capabilities are discouraged. Language requirements may be a proxy for ethnicity, inadvertently eliminating important subgroups from participation.
    - Have interpreters available to participants as needed for discussions, including but not limited to those related to informed consent. Interpreters need not be present on site but may be connected by phone or video conference.
    - Use surveys, questionnaires, and other instruments that have been validated in multiple languages when a choice of instruments is available for a specific domain.
    - Translate and validate research interviews, questionnaires, surveys, and other instruments as relevant to local languages, dialects, and cultural considerations.
        - Surveys that are validated in one language should be translated following standard translation methodology and validated for use.
    - Consider if materials and instruments used in multi-national trials in one country are appropriate for use by speakers of that language in another country.
- Include in the protocol reasonable accommodations for language capabilities including written ability, English (or other native language) proficiency.
    - Scribes may be used for participants who cannot write or write sufficiently.
    - Readers may be used for participants who cannot read or read sufficiently.

[490] For example, consecutive screening (i.e., whereby all potential participants are screened for inclusion) has been reported to be more effective – though more time consuming and therefore perhaps more costly – than risk-based screening (i.e., where only select participants who appear at risk are selected for screening). See Bjørn M, Brendstrup C, Karlsen S, Carlsen JE. Consecutive screening and enrollment in clinical trials: the way to representative patient samples? J Card Fail 1998 Sep;4(3):225-30; discussion 231.

[491] Currently, many industry sponsors cap or do not pay for the expense of documenting screen failures since the process can be so easily abused. IRB/RECs, on the other hand, can require documentation to ensure that all eligible patients are considered for the trial, supporting the ethical principal of justice.

- If a validated instrument is not available for translation, an exception may be made. Otherwise, IRBs/RECs should require adequate explanations for requiring one specific language.
- Ensure that eligibility criteria account for demographic and non-demographic differences in the intended population.

13.4 Feasibility assessments and site selection

KEY SUMMARY

- The feasibility assessment process offers a unique opportunity for a top-down, data-driven approach to estimate and promote diverse representation in clinical trials.
- The feasibility assessment process also offers a unique opportunity for a bottom-up, experience-driven approach whereby communities are engaged at the start of study design and site selection.
- There are two primary components of a feasibility assessment: (1) to assess whether the trial itself is feasible within the country or region identified; (2) to guide deliberate site selection to optimize appropriate representation and trial completion.
- Optimal feasibility assessments utilize multiple data sources to triangulate the capacity of sites to achieve trial objectives, as site responses to traditional feasibility questionnaires often overestimate this capacity.
- Rigorous feasibility assessments should be performed prior to site initiation.
- Following site selection, sponsors and others should support the site in achieving its enrollment and retention goals.

A feasibility assessment involves "evaluating the possibility of conducting a particular…trial … with the overall objective of optimum project completion in terms of timelines, targets and cost."[492] There are two distinctions in a feasibility assessment, both of which are important for inclusion of diverse subpopulations and the successful completion of the clinical trial. The first,

[492] Rajadhyaksha, V. Conducting feasibilities in clinical trials: an investment to ensure a good study. Perspectives in Clinical Research. 2010 Jul:1(3):106-9.

trial feasibility, relates to whether the research study can be successfully conducted in a specific region or country. Trial feasibility considers the study design, availability and use of investigational or marketed product, appropriate comparator, participant type, and incidence of disease or condition in the area. Some trials may simply not be possible in certain settings (e.g., availability of high-end diagnostic imaging equipment, rapid access to a neonatal intensive care unit, prohibitive costs of care, etc.).

The second part of a feasibility assessment is a data-driven individual site assessment that guides informed and deliberate site selection (see "Introduction to Logic Models," "Logic Model: Site Selection" and "Site Selection KPIs" in *Toolkit*). Trial sponsors or their designees (e.g., contract research organizations [CROs]) conduct site feasibility assessments to assess the likelihood of successful and timely recruitment, retention, and data quality. This information can be further informed through partnerships and engagement with the intended communities (see Chapter 8 "Participant and Community Engagement"). Often sites will be asked to complete questionnaires, participate in interviews, and provide data to allow for more objective site selection. Assuming that the feasibility questionnaires are designed for the trial in question and that sites provide accurate responses, predictive modeling[493] of a site's contribution to a multicenter clinical trial could be prepared with this information. The feasibility assessment provides both a preview of a site's capabilities to conduct the study while also establishing the expectations for a site's performance in order to be considered for trial inclusion.

[493] Predictive modeling is a process that uses data mining and probability to forecast outcomes. Each model is composed of predictors or variables that are likely to influence future results. Using these predictors, a statistical model is formulated.

Figure 32: Suggested methods to improve feasibility assessments for diverse inclusion

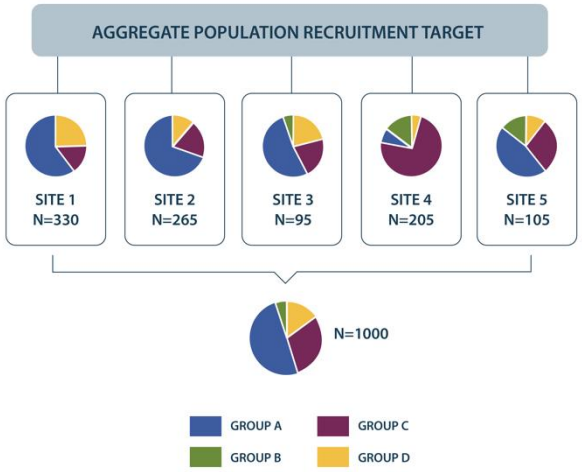
- Incorporate multiple internal and external data sources in enrollment predictions for the intended demographic(s) as enrollment predictions based solely on investigator-provided figures will likely be overestimated.
- Utilize existing data sources (claims data, geo-mapping, competing open trials, commercial databases, etc.) to predict those sites with potential capacity to enroll the intended demographic(s).
- Utilize historical data (publicly available, investigator-provided or from past trials) on investigator or site performance in enrolling the intended demographic(s).
- Leverage predictive modelling to integrate these data sources and predict more precise enrollment figures for the intended demographic(s).

In addition, when assessing the feasibility of a site, the sponsors should consider whether the enrolled population may benefit from the research and, if appropriate, make proactive plans for continued access after the trial to the intervention.[494] Suggested methods to improve feasibility assessments for diverse inclusion are included in Figure 32.

Empirical evidence has shown that sites and investigators routinely overestimate and overcommit the numbers of eligible participants likely to be recruited,[495,496] and this is true prior to consideration of any diversity in enrollment. As a result of these optimistic predictions, recruitment timelines are often unmet or delayed, requiring more sites to be added later and extending the overall time to completion and consequently requiring additional financial resources.[497] While past enrollment figures may provide a basis for better prediction of future enrollment, increasing the precision of these assessments beyond site-reported information is warranted.

[494] https://mrctcenter.org/wp-content/uploads/2017/12/2017-12-07-Post-Trial-Responsibilities-Guidance-Document-Version-1.2.pdf
[495] Johnson, O. An evidence-based approach to conducting clinical trial feasibility assessments. Clinical Investigation. 2015 5(5): 491-99.
[496] Hurtado-Chong A, Joeris, A, Hess D, et al. Improving site selection in clinical studies: a standardised, objective, multistep method and first experience results. 2017. BMJ Open, 7(7).
[497] Cannard, K.G. et al. Recruitment and Retention in Clinical Trials of Deep Brain Stimulation in Early-Stage Parkinson's Disease: Past Experiences and Future Considerations. Journal of Parkinson's Disease. 2018: 421-428.

Figure 33: Visualization of aggregate population recruitment



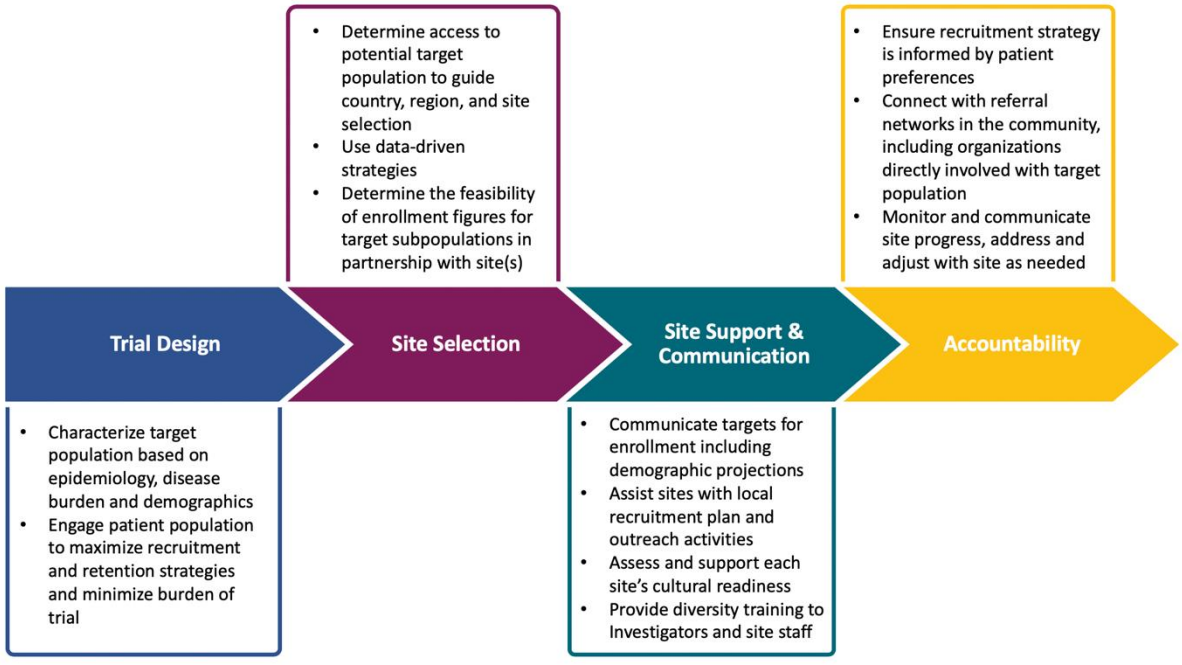
In this example, the planned clinical trial is intended to represent the race/ethnicity of individuals affected by the disease; all the data collected are included for the analysis of the primary outcome. In a single-site trial, therefore, the percentage of diverse representation must be achieved by enrollment at that individual site. In a multi-site trial, however, it is the aggregate of all the sites that is important; any one site may underrepresent or overrepresent a given subgroup. Planning, site feasibility assessment, and dynamic tracking of enrollment is therefore particularly important (note this figure replicates Figure 6 in Part A, Section 2.5 for consistency).

Rigorous, data-driven feasibility assessments offer a unique opportunity for sponsors and CROs to evaluate, understand, and engage in improving the capacity of sites to enroll representative populations in clinical trials and, beyond the numbers of participants, participants of the intended demographic. It is unreasonable to expect every site in a multicenter trial to recruit a diverse population, just as it is unreasonable to expect that every individual trial in a clinical development portfolio will achieve a representative population. Thus, it may be necessary to recruit and select sites that serve a disproportionately high number of minorities to achieve the intended overall enrollment population. See Figure 33 as a visualization of this concept.

To obtain meaningful, evidence-based findings from a feasibility assessment, the availability of data, transparency, and partnership between sponsor/CRO and investigator/site are essential. Optimally, the feasibility assessment would couple site and investigator predictions with data derived from other sources: the site's documented history of performance, competing open trials, commercial databases, geo-mapping, claims data sorted by geography, electronic health records (EHR), etc. Sponsors can identify research sites in communities that have a higher concentration of the subpopulation of interest using accessible data sources. Based on prior data (e.g., demonstrated success by the investigator/site in recruiting a diverse population in completed trials of the same condition), a baseline for the site's capacity to engage, recruit, and

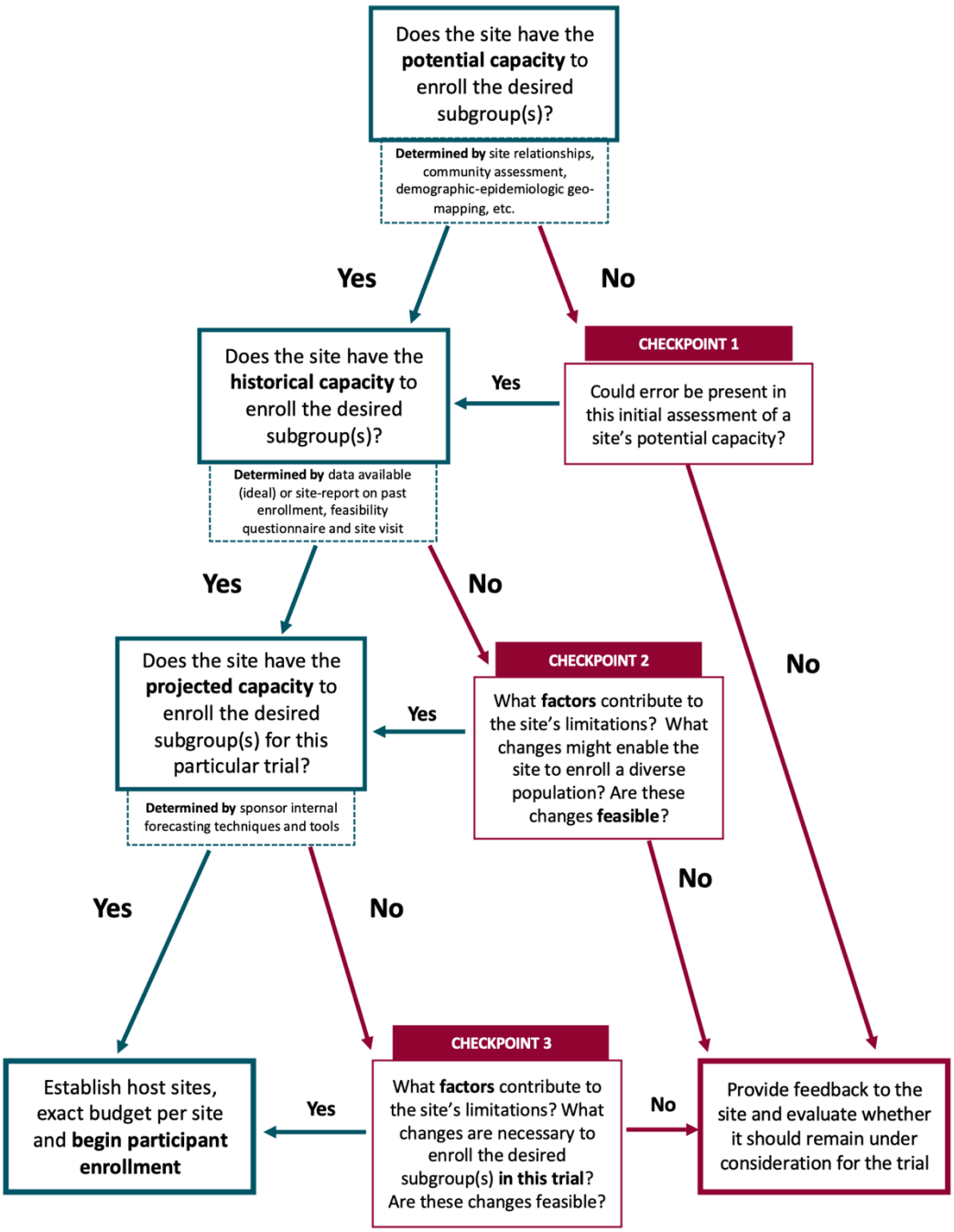
retain certain populations can be established. These data can then be used in statistical modeling to predict site enrollment by demographic tracking. In order to provide accurate predictions for the feasibility assessment, research sites and investigators will use, or will need to develop, systems to collect and report reliable data on the demographics of past enrolled populations. They will also need to deliver upon their estimates. Tracking and monitoring of enrollment progress over time against the site enrollment goal will be helpful. If recruitment is delayed or is comprised of a different demographic than those anticipated by the predicted feasibility assessment, the sponsor or CRO can provide resources (e.g., training, outreach) to improve recruitment in real time. Focused advanced planning – from the start of trial design through site selection, site support and communication, and holding each stakeholder accountable, will help successful enrollment of a diverse patient population (see Figure 34).

Figure 34: Achieving diverse enrollment requires planning, support, and accountability



The MRCT Center Diversity Workgroup developed tools to strengthen realistic feasibility assessments: (1) a feasibility decision tree to guide appropriate site selection, and (2) a checklist for strategic feasibility questionnaire modifications (see "Feasibility Decision Tree" [Figure 35] and "Feasibility Questionnaire Modification Checklist" in *Toolkit)*. Each is geared to provide a high- level decision-making framework that can be adopted and adapted by industry or academic sponsors and CROs for use during the feasibility-assessment and site-selection process. Improving feasibility assessments coupled with statistical modeling and diligent forecasting will increase the probability of timely and successful enrollment of diverse populations.

Figure 35: Feasibility decision tree - a tool to prioritize the recruitment of a representative population during site selection



RECOMMENDATIONS

SPONSORS/CROs

- Leverage public, patient, and health care provider demographic data, including geophysical mapping, disease prevalence, investigator availability, prescriber data, claims data, EHR, etc., to assess the potential population –and subpopulations—with the condition or disease during the trial design phase to guide strategic site selection.
- Obtain geophysical mapping of potential areas to select for research sites with publicly available demographic data.
- Identify research sites in communities that have a higher concentration of the subpopulation of interest (e.g., racial/ethnic minorities, elderly populations, etc.) using accessible data sources.
- Obtain hospital-provided data of patient demographics as well as past overall and demographic-specific subgroup recruitment data in prior clinical trials of the same or similar condition. (Note that prior subgroup recruitment data for a given disease or condition may less helpful if the conditions of the trial are changed from conducting on-site to hybrid or virtual/decentralized. The ability to recruit under these conditions may differ than historical controls.)
- Determine appropriate enrollment figures for subpopulation(s) in partnership with sites, in order to achieve representative diversity in the aggregate across the clinical development portfolio.
- Develop statistical modeling procedures to predict enrollment and retention, refining modeling parameters over time.

SITES

- Understand the data sources needed to estimate the demographic distribution within your own institution.
- Leverage those data sources for feasibility assessments, preferably by condition or disease.

SPONSORS/CROs/INVESTIGATORS/SITES

- Evaluate historical capacity of a site to enroll and retain subpopulation(s) of interest based on previous performance and successful completion of studies. Again, the performance measures of an on-site trial may differ than a hybrid or decentralized trial.
    - Evaluate if sites have a gap in reported potential participant population and historical population recruitment and enrollment.
    - Allocate funding to create strategies to address gaps.

13.5 Study conduct, recruitment and retention

KEY SUMMARY

CONDUCT

- Study conduct relates to the strategies by which the study population and the individual participant are engaged in the research, emphasizing methods to increase the convenience of participation and accessibility of trials.
- Budgeting, planning, and participant engagement are essential for developing and conducting the study, as unique logistical barriers may be faced by particular study populations, resulting in the need for focused and individualized strategies for those populations.
- As much as sponsors and investigators wish enrollment to be representative of the population for which the product is intended, it is important to appreciate that participation in clinical trials is a choice for—and may not be the right choice for—an individual.

- **RECRUITMENT**

- Recruitment, the means by which patients are invited and brought into research studies, is a persistent challenge and costly barrier to a trial's success.
- Underrepresented populations often face unique barriers to participation. Ensuring the enrollment of diverse populations and particular subgroups into research studies requires adoption of specific strategies directed towards those intended populations.
- Recruitment strategy documents (RSD; see "Recruitment Strategy Document Template" in *Toolkit*) are integral to recruitment and are intended to ensure that all stakeholders, including sponsors, CROs, institutions, sites, and investigators are adequately prepared to enroll participants into the trial. These prospective plans provide an opportunity to create the expectation of diverse recruitment in a trial.
    - RSDs should be developed considering available epidemiological data, as applicable, and in advance of implementation.
    - Ongoing and dynamic monitoring should be built into the RSD, and contingency plans prepared in advance, so that timely interventions at site(s) can be made to

improve enrollment if enrollment (or the demographics of predicted enrollment) deviates from the strategy document.

  - In multi-site trials, tailored RSDs should be provided to individual sites, describing that site's intended population for the trial based on an understanding of the aggregate trial population demographics required and the capacity of that individual site to enroll particular subpopulations, determined cooperatively during a diversity-driven feasibility assessment.

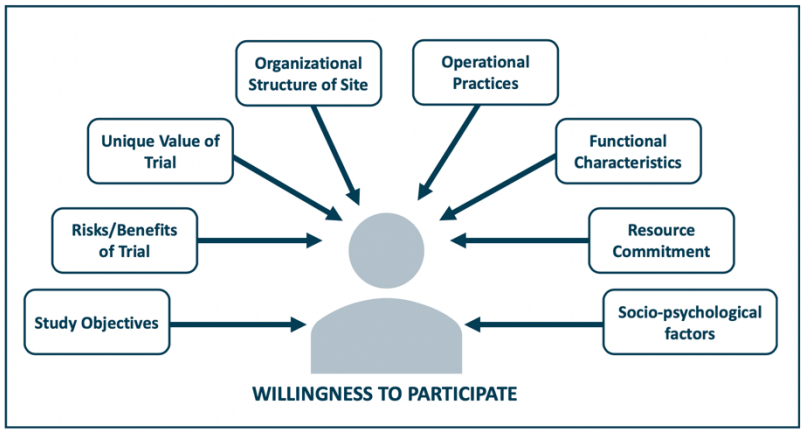
- There are cultural differences in attitudes towards participation in clinical trials. Understanding and addressing cultural differences can bolster recruitment and build a foundation of trust and respect.

- **RETENTION**

- The overall aim is for every participant to complete the study, and every effort should be made to make it possible for the participant to remain in the study. Understanding, appreciating, and responding to the participant experience are necessary.
- Retention of diverse subpopulations requires adoption and testing of different strategies, as retention of one subpopulation may not translate to successful retention for a different subpopulation.
- Communication is key to retention. Clear, complete, comprehensive communication and education at the time of recruitment and enrollment improves participant retention in research. An individual who understands the study's purpose, what it means for their treatment and health, and what to expect during the study is more likely to adhere with the expectations of the study.

Study conduct involves implementing the planned study protocol, considering recruitment of potential participants and retaining enrolled participants. An individual's willingness to enroll and participate in clinical research will depend not only on the study objectives, risks and benefits of the trial, and what participation of the trial might offer that is not otherwise available outside the research. It will also depend, at least in part, on the logistical and practical characteristics of the research such as the organizational location and structure of the site (e.g., regional hospital, private health center, small clinic, physician offices), operational practices (e.g., hours of clinic operation, availability of weekend or after-work hours, type of clinician involved), the functional characteristics of the trial (e.g., the number and location of trial visits, whether visits are on-site or virtual), resource commitment (e.g., time to participate, child care, reimbursement, payment), and socio-psychological factors (e.g., historical experiences, trust between clinician and patients) (see Figure 36). Furthermore, factors that influence willingness may vary based on race or ethnicity, disease status, socio-economic status and other demographic and non-demographic variables.[498,499] Yet studies suggest that when invited to participate in research, racial and ethnic minority consent rates are similar to those of non-

Figure 36: A potential participant's willingness to participate in clinical research is influenced by many factors



[498] Bonevski, B. et al. Reaching the hard to reach: a systematic review of strategies for improving health and medical research with socially disadvantaged groups. BMC Medical Research. 2014, 14:42

[499] Christie J, Itzkowitz S, Lihau-Nkanza I, Castillo A, Redd W, Jandorf L. A Randomized Controlled Trial Using Patient Navigation to Increase Colonoscopy Screening among Low-Income Minorities. Journal of the National Medical Association. 2008. Vol 100(3): 278-284.

minority populations.[500] Study conduct and implementation, therefore, need to consider all the relevant variables that may influence the intended population's choice to participate.[501]

Trial conduct includes a wide range of considerations from behavioral interactions and communication to more practical logistics, such as transportation, childcare, time requirements and study visit schedule, clinic hours, disability access, off-site availability (by telephone or video visit, mobile application, visiting nurse, etc.), among others; overall, these will influence retention of participants.

The ability for any researcher to recruit and retain diverse populations requires an understanding of the desired population (e.g., cultural considerations, patient perspectives, and communities' needs). The need for participant input, not only for study design but to advise on study implementations challenges, underscores the importance of early community and participant engagement.[502]

[500] Wendler D, Kington R, Madans J, Van Wye G, Christ-Schmidt H, et al. (2006) Are racial and ethnic minorities less willing to participate in health research? PLoS Med 3(2): e19.
[501] Dilworth-Anderson, P. Introduction to the Science of Recruitment and Retention Among Ethnically Diverse Populations. The Gerontologist. 2011. Vol 51. S1-S4.
[502] Sugden, NA, Moulson, MC. Recruitment strategies should not be randomly selected: empirically improving recruitment success and diversity in developmental psychology research. Frontiers in Psychology. 2015; 6(523).

Unique strategies may be needed to address different operational and logistical barriers for different populations (see Figure 37 Case Example: *Gender, Race and Clinical Experience Study: GRACE*).[503] For example, a study seeking enrollment of post-partum depression in young mothers should be implemented differently than a study that is seeking to recruit Alzheimer's patients – the provision of childcare will be valued differently in different populations. Thoughtful planning, appropriate budgeting, and intentional considerations will help potential and enrolled participants feel welcomed and anticipated.

Figure 37: Case example for targeted recruitment in the Gender, Race and Clinical Experience (GRACE) study

The Gender, Race and Clinical Experience Study (GRACE)[64] was a Phase IIIb study designed specifically to enroll and retain women of color in an antiretroviral clinical trial. Strategies prioritized by the sponsor, Tibotec Pharmaceuticals, were to include sites in areas of high HIV burden among women of color and sites that actively treated women of color living with HIV, whether or not they had been involved in clinical research before. In addition, the sponsor implemented targeted recruitment strategies at sites, such as requiring sites to enroll a certain number of women before enrolling men and requiring sites to maintain a majority of women enrolled. The sponsor hired patient advocates as community "consultants," who actively connected study sites to community-based groups and local resources throughout study implementation. The strategic branding of the GRACE study and targeted media campaigns within communities of color are additional reasons for its success. In terms of retention, transportation stipends were provided and actively promoted throughout the study, and modest grants were available to sites to fund events that could foster the retention of participants. GRACE successfully met its recruitment goals on time and recruited 429 patients, of whom 67% were women, the majority of whom were of color (87%). Sponsor-provided support for sites was credited as a major contributor to the successful engagement of the trial's diverse population.

Below, we consider impediments and approaches to improve study recruitment and retention, through the development and provision of a recruitment strategy document (RSD; see "Recruitment Strategy Document Template," "Introduction to Logic Models" and "Logic Model: Recruitment Strategy" in *Toolkit*), with a particular focus on the inclusion of populations that are underrepresented or underserved in research. There is no

[503] Falcon, R., Bridge, A., Currier, J., et al. (2011). Recruitment and retention of diverse populations in antiretroviral clinical trials: practical applications from the Gender, Race And Clinical Experience study. *Journal of Women's Health, 20*(7): 1043-1

"one-size fits all" approach to addressing issues related to diverse participation in clinical research; many barriers and potential solutions are overlapping and interrelated.[504] Therefore, while we offer suggestions and considerations for recruitment and retention, they are not discrete and are often broadly applicable in a research study.

13.5.1 Recruitment and recruitment strategy document

Recruitment is the means by which potential participants are invited and brought into research studies. Recruitment is a challenging and costly necessity for a trial's success;[505,506] the complexity of recruitment increases when recruiting and enrolling underrepresented, vulnerable, or otherwise difficult-to-reach populations. Impediments faced by underrepresented populations during recruitment are well documented[507,508,509] and range from psychological factors (e.g., trust, fear) to practical barriers (e.g., technology, transportation, translation of the consent document). How patients are recruited into research studies requires strategic planning of specific activities towards the population of interest.

Formulating a detailed and targeted **recruitment strategy document** (RSD), supported by appropriately trained personnel and financial resources, will help sponsors and investigators track and achieve the intended population (see "Recruitment Strategy Document Template" and "Recruitment Strategy KPIs" in *Toolkit*). A study RSD is a strategic guidance document, tailored to a department within an institution or to the specific research study, that contains

[504] Sood JR, Stahl SM. Community Engagement and the Resource Centers for Minority Aging Research. *The Gerontologist*, Volume 51, Issue suppl_1, June 2011, Pages S5–S7, https://doi.org/10.1093/geront/gnr036
[505] Treweek S, Pitkethly M, Cook J, Fraser C, Mitchell E, Sullivan F, Jackson C, Taskila TK, Gardner H. Strategies to improve recruitment to randomised trials. *Cochrane Database of Systematic Reviews.* 2018, Issue 2. Art. No.: MR000013. DOI: 10.1002/14651858.MR000013.pub6
[506] Morain S, Largent E. Recruitment and Trial-Finding Apps-Time for Rules of the Road. Journal of the National Cancer Institute. 2019 111(9), 882-886.
[507] Ford JG, Howerton MW, Lai GY, Gary TL, Bolen S, Gibbons MC, Tilburt J, Baffi C, Tanpitukpongse TP, Wilson RF, Powe NR. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2008 Jan 15;112(2):228-42.
[508] Hudson S. V., et al. Physician perspectives on cancer clinical trials and barriers to minority recruitment. *Cancer Control*. 2005; 12(Suppl 2):93-6.
[509] 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. American journal of public health. 2014 Feb;104(2):e16-31.

operational objectives, suggestions, and contingency plans for participant enrollment (see "Recruitment Contingency Action Plan" in *Toolkit*), corrections for any deviation from the plan for the specific participating site and, if a multi-site trial, for the trial as a whole. The RSD should address anticipated barriers and approaches to overcome or mitigate those barriers. Good planning and preparation can lead to successful and timely recruitment; failure to do so may lead to unmet recruitment goals, protocol amendments, addition of sites, and costly trial extensions.[510] One company's efforts to develop demographic plans for both the specific trial and the overall product development lifecycle to achieve diverse recruitment is a useful example (see "Case Study: Focusing on Global Clinical Diversity as a Priority Point" in *Toolkit*.)

The development of detailed recruitment strategy documents helps to ensure that all stakeholders, including sponsors, CROs, institutions, sites, and investigators, are adequately prepared for participant recruitment enrollment. In the context of enrolling a diverse population, and when epidemiological data are available (e.g., census data; the Incidence and Prevalence Database[511]), ranges for the intended subpopulations may be recommended in the recruitment strategy document. This is in line with the ICH E17 guidelines – where the concept for establishing appropriate stratification and regional sample size is noted as differences in response to treatment can be explained by differences in ethnic distribution in regions. It should be noted that the granular data needed to be optimally informative does not exist for every disease or condition, in all locations, and arrayed by demographic and non-demographic categories. The epidemiology of many diseases is incomplete or has been subject to bias. A commitment to data collection across geographies and in underrepresented populations is necessary (see Part D "Data Standards and Analysis").

In a multi-regional, multi-site study, specific RSDs should be provided to individual sites and, optimally, their feedback should be incorporated. Site-specific RSDs are often considered supplemental material provided to sites after the study's feasibility assessment and the selection of participating sites but prior to study initiation. Site RSDs should include information

[510] Cannard GK, Hacker ML, Molinari A, Heusinkveld LE, Currie AD, Charles D. Recruitment and Retention in Clinical Trials of Deep Brain Stimulation in Early-Stage Parkinson's Disease: Past Experiences and Future Considerations. Journal of Parkinson's disease. 2018 Jan 1;8(3):421-8.
[511] Incidence and Prevalence Database (IPD) [Internet]. Clarivate Analytics. May 2, 2020. Available online: http://www.tdrdata.com/(S(olbqodtelrgj2wg51rprg4do))/ipd/ipd_init
[Accessed 22 June 2020).

about the site's population profile in relation to the study question, as well as the specific local subpopulations. Whenever possible, site-specific plans should incorporate data collected during feasibility assessments regarding a site's stated capacity to engage, recruit, and retain certain populations. These data can drive the site-specific recruitment document to the populations by subgroups of interest, with the goal of increasing the overall representativeness of the trial population. Transparent and collective understanding of recruitment and retention documents will optimize performance.

Essential components to include in study and site recruitment strategy documents are communication pathways and processes, timelines, realistic metrics of progress, and mechanisms for monitoring and evaluating enrollment and retention.[512] The RSD should outline the details for recruitment outreach activities and communications, including direct (i.e., face-to-face interactions such as door-to-door visits, physical presence in a clinic or community space) and indirect methods (i.e., communications without direct personal interaction such as adverts, email, post mail, billboards). Table 11 provides a detailed list of outreach and communication activities.

Table 11: Recruitment outreach and communication activities

DIRECT	INDIRECT

• Places of worship
• Recruitment tables at clinics, community centers, sporting events, meeting places
• Study staff placed in health care settings
• Physician/provider referrals
• Health fairs
• Town hall meetings
• Employee and student referrals
• Phone calls or door-to-door visits
	• Advertisements
	  ○ *Traditional*: mail recruitment flyers, info sheets, billboards, posters, newspapers, bus stop signs, press releases
	  ○ *Digital*: social media, study-specific websites (search engine optimization)
	• Health bill inserts

[512] Huang GD, Bull J, McKee KJ, Mahon E, Harper B, Roberts JN. Clinical trials recruitment planning: a proposed framework from the clinical trials transformation initiative. Contemporary clinical trials. 2018 Mar 1;66:74-9.

• Neighborhood locations (e.g., barber shops) • Patient-powered networks (e.g., ResearchMatch, https://www.researchmatch.org/)	• Study branding • Advocacy organizations and groups • Disease-focused foundations • Patient-to-patient referrals • Family member-to-family member referrals • Identification through medical records, EHR, publicly available records • Listing on ClinicalTrials.gov, ICTRP.org

Ongoing and dynamic monitoring permits timely site interventions if actual enrollment does not meet expected enrollment, or if the actual enrollment does not reflect the expected demographics intended for the study (see "Case Study: Achieving and Exceeding Clinical Trial Participant Diversity Targets" in *Toolkit*). Early monitoring allows the sponsor to implement contingency plans (e.g., modification of advertisement methods, expansion to additional sites) defined at the outset for timely execution of the study and fulfilment of demographic enrollment goals.

The MRCT Center Diversity Workgroup developed practical elements to help guide sponsors in creating trial-level recruitment strategy documents to increase diverse representation in clinical trials (see Table 12). An example of a RSD, tailored to prompt consideration of underrepresented populations, is available in the *Toolkit*.

Table 12: Elements to consider within a trial-level recruitment strategy document

RECRUITMENT DOCUMENT ELEMENT	JUSTIFICATION
Trial sample size (N) calculation to achieve treatment effect as provided in protocol	Typical power calculation included in recruitment planning to provide the goal for overall study population across all sites

Overall epidemiology of disease	Available measures of disease frequency (prevalence, incidence, etc.) to characterize the burden of disease by geographic region
Epidemiology of disease by demographic	Measures of disease frequency (prevalence, incidence, etc.) by available demographics and by region, to highlight the subpopulations for whom the intervention is intended
Heterogeneity assessment across subgroups and effect on sample size	Assessment based on literature, ongoing trials, or prior evidence for differences in disease manifestation or treatment response in particular subpopulations, to justify modified methods for recruitment, sample size and analyses of the intended subpopulations.
Potential limiters and enablers for strategic recruitment	Logistical, economic, capacity-related, and sociocultural elements that might enable or limit recruitment in particular subpopulations or regions
Diversity guidelines and subpopulations for trial	Development of objectives to achieve a diverse trial population, with overall trial-level enrollments for specified subpopulations, to highlight recruitment expectations

Outside of study- and site-specific RSDs, local institutions and IRBs/RECs should also develop and be familiar with recruitment and retention strategies unique to their catchment area and specific study populations. As highlighted in Part C, "Broadening Engagement," a number of social considerations and impediments can be addressed by establishing a presence in and building a relationship with communities. And, in addition to community and patient physician

referrals,[513] *effective* recruitment and retention strategies are often linked with community outreach activities, built upon relationships with community members and their leaders.[514,515]

Figure 38: Explanation of community-based participatory research (CBPR) models

Community-based participatory research (CBPR)[78] uses community involvement beyond the individual participant level. Research that employs CBPR engages community members as partners, involving them at every stage in research – from study question, design, recruitment and implementation, data collection, to interpreting, delivering and effectively communicating findings and results – and is often used in post-market research to answer questions of importance to the community (policies or social changes that may benefit the community). The CBPR model is based on the theory that engaging community members as collaborators will improve a population's participation, enthusiasm and retention; a systematic review of studies using the CBPR model found an 89% success rate in maintaining engagement in communities with the intervention.

For studies aiming to enroll underrepresented populations, the overall recruitment strategies should be selected to meet the particularities of the intended subpopulation.[516] Community-based participatory research (CBPR) models represent a partnership-based approach that equitably involves community members, organizational representatives, researchers, and other stakeholders in all aspects of the research study (see Figure 38). [517]

[513] Hudson S. V., et al. Physician perspectives on cancer clinical trials and barriers to minority recruitment. *Cancer Control*. 2005; 12(Suppl 2):93-6.
[514] Winter SS, Page-Reeves JM, Page KA, Haozous E, Solares A, Nicole Cordova C, Larson RS. Inclusion of special populations in clinical research: important considerations and guidelines. *J Clin Transl Res*. 2018 Apr 7;4(1):56-69.
[515] Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggly S. Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. Cancer Control. 2016 Oct;23(4):327-37.
[516] 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. American journal of public health. 2014 Feb;104(2):e16-31.
[517] De las Nueces D, Hacker K, DiGirolamo A, Hicks LS. A systematic review of community-based participatory research to enhance clinical trials in racial and ethnic minority groups. Health Serv Res. 2012;47(3 pt 2): 1363---1386.

In essence, CBPR models help build trust and reciprocal partnerships between those implementing the research activities and the community and its members. Establishing community relationships aids in developing recruitment strategies for a representative population.[518,519,520] When recruitment materials resonate with individuals and their communities, they are more likely to participate (see Figure 39– SeniorWISE).[521,522] This may mean translating recruitment materials, having interpreters available to answer any questions a participant may have, using culturally relevant and applicable materials, and placing relevant research materials in appropriate places (see Table 13).

Figure 39: Example of appropriate messaging and recruitment strategies through the SeniorWISE study

The SeniorWISE (Wisdom is Simply Exploration) study investigated the effect of memory training and the progression of Alzheimer's disease in a tri-ethnic study population of Hispanic/Latino, African American and Caucasian adults over the age of 65. Because minority elders are often difficult to recruit into studies, the study team tailored its recruitment strategy and placed its researchers where the older population lived and/or frequented (i.e., senior centers, wellness centers, churches, etc.). The research team involved directors of the senior centers, who acted as cultural gatekeepers and helped train local staff on the importance of the research study and how to reduce the stigma of Alzheimer's disease by talking about it. Because the study team focused their efforts on providing easy and feasible access, culturally and age-appropriate messages, and built trust through using community gatekeepers, the study was able to recruit and retain its target population with a 90% success rate.

[518] De las Nueces D, Hacker K, DiGirolamo A, Hicks LS. A systematic review of community-based participatory research to enhance clinical trials in racial and ethnic minority groups. Health Serv Res. 2012;47(3 pt 2): 1363---1386.
[519] UyBico SJ, Pavel S, Gross CP. Recruiting vulnerable populations into research: a systematic review of recruitment interventions. J Gen Intern Med. 2007;22(6):852--863.
[520] Dilworth-Anderson, P. Introduction to the Science of Recruitment and Retention Among Ethnically Diverse Populations. The Gerontologist. 2011. Vol 51. S1-S4
[521] Austin-Wells, V, McDougall, G.F., Becker, H. Recruiting and Retaining an Ethnically Diverse Sample of Older Adults in a Longitudinal Intervention Study. Educational gerontology. (2006) 32 159-170.
[522] McDougall, G.F., Simoson, G., Friend, M.L. Strategies for Research Recruitment and Retention of Older Adults of Racial and Ethnic Minorities. Journal Gerontology Nursing. 2015. 41(5) 14-25

Table 13: Strategies to tailor recruitment materials for underrepresented populations

- Ensuring linguistic and cultural appropriateness of materials for intended participants
- Mail alerts to minority physicians
- Social media postings optimized for underrepresented and undersered populations
- Study materials translated into primary languages of participants
- Bilingual staff or translators available
- Bilingual participant navigator
- Informed consent with visual imagery
- Cultural competency and implicit bias training for staff
- Outreach to minority health professional groups and family, community physicians
- Outreach to faith-based organizations
- Receptionist and call center operator training

Tailoring recruitment materials, perhaps by drafting recruitment transcripts with potential participants and pilot testing on the intended populations, will help researchers effectively communicate with the desired participant population. Intentional communication for recruitment is important and can be delivered in either direct or indirect ways (see above Table 11 "Recruitment outreach and communication activities")– whether that be via a clinical provider's support or through advertisements that address the population's—and subpopulations—health concerns.

Recruitment is dependent upon study design and specifically inclusion and exclusion criteria (see Section 13.3 "Eligibility criteria"). While eligibility criteria may influence the strategy for recruitment,[523] addressing logistical and operational barriers will drive success, and potential participants can help to identify those barriers. Where communications (e.g., recruitment materials) are placed and prioritized, how the messages are crafted, where the trial is located for participants to enroll, and the time associated for any given participant will depend upon the populations. Strategies for recruitment need to be tailored to the population(s) of interest.

[523] Huang GD, Bull J, McKee KJ, Mahon E, Harper B, Roberts JN. Clinical trials recruitment planning: a proposed framework from the clinical trials transformation initiative. Contemporary clinical trials. 2018 Mar 1;66:74-9.

Table 14: Data-driven recruitment strategies

- Tracking methods of referral and referral source
- Tracking each point of contact for participants
- Efficient pre-screening methods (e.g., call-in center)
- Scheduling first screening visit and time commitment (see "Participant Time Commitment Model" in *Toolkit*)
- Tracking incidence of and reasons for screen failures (see "Screen Failure Tracking Log" in *Toolkit*)
- Tracking of recruitment and enrollment (see "Eligibility and Enrollment Log" in *Toolkit)*
- Tracking incidence of and reasons for patient refusals

It is important to assess and quantify recruitment methods so that effective data-driven strategies of recruiting the intended populations are improved over time (see Table 14). Measurement of each step in recruitment will help refine recruitment strategies for future clinical trials, define the effectiveness of referral sources, and modify methods should remedial measures to increase enrollment be necessary. Measurement, tracking, and analysis will take resources, planning, and effort but will help identify successful recruitment strategies of the appropriate subgroup populations.

RECOMMENDATIONS – RECRUITMENT

SPONSORS / CROs

- Use the product development plan to reflect the intended demographic population (based on the intended use-population, epidemiology of disease, etc.), and then plan the portfolio of trials accordingly. The recruitment strategy document for each individual trial should refer to the overall plan to guide each study, updating the overall plan and the portfolio as data are gathered.
- Develop an individual trial recruitment strategy document considering not only the sample size for the trial but also the subpopulation profile within the trial, based on the epidemiology of the disease and/or the intended population to use the intervention.
    - Engage with the community and potential participants during the study design phase
    - Create a diverse patient and/or community advisory board.
    - Establish partnerships with local clinicians to help investigators/sponsors/CROs navigate recruitment of community members into the study.
    - Consult with patients, providers, and staff prior to study implementation to discuss the planned research study and identify potential barriers to recruitment.
    - Use focus groups and personal interviews to understand potential participant, care provider, and clinical staff barriers to recruitment and to identify better avenues for recruitment.
- Develop a site-specific recruitment strategy document, co-created with the site investigator and study team, using the information gathered in the feasibility assessment, including:

  - The site subpopulations and overall population for which they have capacity to enroll and to which they are committed, in consideration of the trial-level recruitment strategy document.
  - Detailed methods for communications, outreach, and advertising for the trial.
  - Screening procedures and accommodations for individual participant requests.
  - Anticipated barriers and contingency plans.
  - Thresholds and timelines for evaluating progress and implementing contingency plans for slow or failed efforts.
  - Set recruitment milestones and evaluation points in the study timelines. Adapt approaches, if necessary, if enrollment goals are not met.
- Understand costs of and designate study budget for recruitment activities.
- Track recruitment steps, successes, and challenges.
- Monitor recruitment conversion rates compared to what was indicated by the site feasibility assessment and overall study recruitment strategy document.
- Continue to engage those involved in recruitment to trouble-shoot and address problems as they arise throughout implementation of the trial.

IRBs

- Develop an index of recruitment and retention strategies unique to the institution and its specific study populations.
- Provide a prototype recruitment and retention strategy document for investigators to emulate.
- Create and share model tracking and monitoring tool for enrollment and retention (particularly for the underrepresented and underserved populations) with investigators.
- Review summary of overall trial plan and site(s)-specific plans based on epidemiology of disease and intended use population.
- Examine enrollment demographic characteristics compared to plan at continuing review.
- Request remediation plan if enrollment deviates from plan significantly.

SPONSORS / CROs, INSTITUTIONS / SITES / INVESTIGATORS

- Provide tailored recruitment materials to staff and providers to help support their communication with potential participants.
- Understand local costs of and designate a study budget for recruitment activities.
- Pilot test recruitment approaches (i.e., flyers, advertisements, brochures).
- Use multiple and complementary approaches for recruitment which may be more effective than one single avenue or strategy.
    - For example, consider engaging the different spheres of influence (e.g., family, friends, caretakers, community members and health care providers) to create trust in and understanding of the purpose of the research.
- Use community outreach, educational, or community-based programs coupled with social media marketing as a comprehensive model for recruitment and retention.

13.5.2 Study conduct and retention

Retaining a participant throughout the study protocol is critical for study completion, analysis, and reporting of results. The longer a participant is in a research study, the more valuable their information. Retention of underserved and underrepresented populations in research may require different strategies: successful retention of one population may not translate to successful retention for a different population. Impediments to retain a diverse participant population in a research study include those related to logistics: transportation, work-hour considerations, study visit constraints, elder- and child-care, and out-of-pocket expenses. Understanding and addressing participants' logistical challenges from the outset may increase their willingness to continue to be involved in research and their overall satisfaction with the experience. Identifying strategies to maximize retention rates in advance of study implementation, with specific attention to minimizing inconvenience and burden will help reduce participant attrition (see Table 15 and "Logic Model: Recruitment, Conduct and Retention" and "Recruitment, Conduct and Retention KPIs" in *Toolkit*).

Table 15: Retention strategies to minimize inconvenience and reduce burden

- Provide information to communities, (e.g., health fairs, local screening centers)
- Minimize in-person visits, if possible:
  - Use of mobile technologies
  - Telemedicine and video visits (note: sites and sponsors will need to take into account the different communities' familiarity and access to these technologies)
  - Home health visits, phlebotomist home visit
  - Local clinical site for routine procedures (e.g., blood test, routine imaging)
- Convenient locations for visit
- Individualized study calendar for appointments and research procedures
- Flexible timing of appointments
- Flexible clinic schedule (e.g., after-hours and weekend visits)
- Clinic conveniences: efficient procedures, comfortable waiting areas, snacks and drinks
- On-site child-care or eldercare, if on-site visit required
- Transportation assistance:
  - Arrangements for taxi, bus, van, rideshare companies, etc.
  - Valet parking
  - Car rental assistance

    - Flight and hotel arrangements
- Vouchers for food
- Appropriate reimbursement for expenses, including consideration of missed time at work, and family member or caregiver expenses if necessary for participant visit
- Provision of *letters of participation* for employees to provide to employers
- Welcome kits with instructions, maps, directions, information about study team
- Pre-packaged study kits if special supplies are necessary
- Health literate information available in appropriate languages
- Large print information

Retention strategies can include flexible study hours and study locations or virtual visits, provision of childcare and food during study visits, transportation assistance, appropriate reimbursement, and other accommodations (see Figure 40 "Example of reducing participant burden through transport provision by rideshare"). [524,525] Appropriate reimbursement for expenses of participation is particularly important for individuals who are economically disadvantaged; fair payment or compensation should be offered to everyone (see Section 13.6 "Payment").

Figure 40: Example of reducing participant burden through transport provision by rideshare

In a study investigating the impact of acute alcohol intoxication on waterpipe smoking patterns and toxicant exposure, rideshare services were used to address potential barriers in continued participation in the study. The study involved two site visits for participants, each lasting up to two hours. To encourage participant engagement, study staff made regular calls to participants, provided fair compensation (U.S. $125 per visit), and offered additional compensation (U.S. $20) for completing both study visits. In addition, the study provided transportation to and from study visits via a rideshare service. Participants reported the provision of rideshare services was important in their decision to complete all study visits. In this study and despite a challenging population, the retention rate was greater than 95%.

Each demographic of the intended participant group may have its own needs. For instance, in planning a study for disabled individuals, handicapped accessible sites will be necessary; if studying an intervention to slow the progression of dementia, the accessibility and needs of the participant's caregiver(s) should be considered; if the study site is located in and serves a predominantly Chinese or Spanish-speaking community, appropriate translation of all materials and access to interpreters will be necessary. Identifying barriers in advance of implementation will give sponsors, investigators, and study teams an opportunity to prepare solutions, plan budgets, and configure contingency plans if recruitment or retention are not aligning to expectations.

[524] Leavens ELS, Stevens EM, Brett EI, Molina N, Leffingwell TR, Wagener TL. Use of Rideshare Services to Increase Participant Recruitment and Retention in Research: Participant Perspectives. J Med Internet Res 2019;21(4):e11166
[525] Oh SS, Galanter J, Thakur N, Pino-Yanes M, Barcelo NE, White MJ, de Bruin DM, Greenblatt RM, Bibbins-Domingo K, Wu AH, Borrell LN. Diversity in clinical and biomedical research: a promise yet to be fulfilled. PLoS medicine. 2015 Dec 15;12(12):e1001918.

Despite the best planning effort, no investigator or study coordinator can know the particular circumstances of each participant; consultation from an expert on recruiting a specific population may be needed. We recommend during the screening process, throughout consent, immediately following enrollment, and continuously throughout the trial, that a member of the study team has a direct conversation with the participant. That conversation should be open and respectful, will depend on the needs and expectations of the study, and can begin an open-ended question such as, "Is there anything that we should understand to help make your participation easier?" An interview protocol to standardize this conversation may be helpful. The conversation should be a non-judgmental, objective moment to ask about responsibilities at home (e.g., elder- and child-care), transportation concerns, work concerns, religious practices, and other practical impediments to successful participation. The study team will then be in a position to address those issues and offer recommendations, and perhaps assistance or reimbursement, if possible. It is also a good time to develop a study schedule and to ask about preferred methods of communication; internet access; permission to contact family members, friends, referring physicians and others; intercurrent health care concerns; and other questions. Providing for open communication and, as appropriate, documenting in the informed consent form (ICF) the supportive mechanisms available for the participant, is preferable to making assumptions about the participant's lifestyle, habits, or needs; is particularly important when the participant is from a cultural background different from the investigator or study team; and sets the stage for further conversations as issues arise during the study.

> *"Is there anything that we should understand to make your participation easier?"*

Maintaining contact through regular communication with participants has been cited as an important measure for retention.[526] Each participant should be asked for their preferred form of communication (e.g., in-person, phone conversation, text message, email, letter, etc.), while

[526] Bonevski B, Randell M, Paul C, Chapman K, Twyman L, Bryant J, Brozek I, Hughes C. Reaching the hard-to-reach: a systematic review of strategies for improving health and medical research with socially disadvantaged groups. BMC medical research methodology. 2014 Dec;14(1):42.

maintaining privacy. It may be worthwhile to ask the participant for an additional contact(s) should that person be unavailable and obtain permission to contact the individual(s) identified, if necessary. Utilizing patient navigators, "gatekeepers," or "study buddies" is one way to maintain connection with participants, and has been piloted with the elderly and those of lower socioeconomic status, and for trials with complex protocols (i.e., cancer treatment trials).[527,528,529] Patient navigators are trained to establish a relationship with the participant to maintain engagement, answer questions, allay concerns, and periodically provide new information pertinent to participating in research. Depending on the complexity of the study (e.g., number of visits) and the information that needs to be shared, patient navigators are often clinically trained professionals. In simpler studies, the study buddy may be a family members or designated friend.

Clear, complete, comprehensive communication and education at the time of recruitment and enrollment improve participant retention in research.[530] Participants cannot comply if they do not understand what is expected of them. Clear communication, using plain language, numeracy, and visual imagery to simplify instructions and expectations is helpful.[531] Maintaining frequent and positive interactions with the participant may also promote trust with the study team.

[527] Hughson JA, Woodward-Kron R, Parker A, Hajek J, Bresin A, Knoch U, Phan T, Story D. A review of approaches to improve participation of culturally and linguistically diverse populations in clinical trials. Trials. 2016 Dec 1;17(1):263.
[528] Christie, J. et al. A Randomized Controlled Trial Using Patient Navigation to Increase Colonoscopy Screening among Low-Income Minorities. Journal of the National Medical Association. 2008. Vol 100(3): 278-284.
[529] https://jons-online.com/issues/2018/september-2018-vol-9-no-9/1976-recruiting-and-retaining-minorities-in-oncology-clinical-trials-a-nurse-navigator-perspective
[530] 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. American journal of public health. 2014 Feb;104(2):e16-31.
[531] See for instance, MRCT Center Health Literacy in Clinical Research. Available at: https://mrctcenter.org/resources/?project=health-literacy-clinical-research [Accessed 22 June 2020]

RECOMMENDATIONS – STUDY CONDUCT AND RETENTION

INVESTIGATORS / SITES

- Train study staff in cultural competency to identify and address implicit bias (see Chapter 10 "Workforce and Diversity: Training and Development").
    - Use interview protocols to standardize conversation and questions to help neutralize biases.
- Recruit and support study staff of diverse backgrounds.
- Build and maintain rapport with the participant and participant influencers (i.e., caregivers, family members, community).
    - Train study staff on what it means to be accommodating to a participant's varying needs.
    - Train study staff to be sensitive to the participant's needs.
    - Encourage sympathy and empathy towards the participant.
    - Respect the autonomy of the participant; listen carefully and repeatedly ask if anything is unclear.
        - Use teach-back: ask the participant to explain what he or she understood.
    - Allow sufficient time for study visits so that the participant has the opportunity to engage and for relationships to form.
    - Maintain contact and connectivity with participant.
    - Document interactions and details of conversations with participants to provide consistent level and style of interaction.
    - Maintain consistency in the study personnel who interact with participants, if possible.

SPONSORS / CROs / INVESTIGATORS / SITES

- Be flexible in scheduling and conducting study follow-up visits.
    - Create a study schedule soon after enrollment so the participant understands their scheduling commitments.

- Consider what additional family obligations or social responsibilities the participant may need to manage in order to participate in the clinical trial.[532]
- Offer choices to participant enabling control and autonomy over their schedules if data integrity is not impaired:
  - Provide flexible follow-up visit dates.
  - Provide alternative hours for clinic operations (e.g., after normal shift-work hours, weekends).
  - Provide transportation and parking, or reimbursement for transport to and from clinic visits.
  - Provide mobile phone / calling card / voucher for calling.
  - Provide various locations for follow-up visits to maximize convenience.
  - Offer virtual visits (e.g., telehealth, video conferencing).
  - Utilize visiting nurses and home visits.
  - Optimize local sites for routine procedures (e.g., blood draws).
  - Consider particular health and mobility issues for participants such as the elderly, chronically ill, disabled, young, isolated, or otherwise dependent as they may need special considerations for transportation (e.g., handicap accessibility, elevators, etc.).

- Enable study site accessibility (provide directions to the study site, study building, and the study room that are clear and easy to follow, and consider handicap accessibility).
- Determine whether and which study visits can be virtual, accommodated by a visiting nurse, or performed at a local site.
  - Give patients access to trials or trial visits in their homes or at a local clinic, health center, or office to reduce overhead costs and eliminate geographical barriers, transportation costs, and scheduling difficulties.[533]

[532] Otado J, Kwagyan J and Osafo N. Culturally competent strategies for recruitment and retention of African American populations into clinical trials. Clinical and Translational Science. 2015; 8(5): 460-466.
[533] U.S. FDA. Dialogues on diversifying clinical trials: successful strategies for engaging women and minorities in clinical trials. September 2011. https://www.fda.gov/files/science%20&%20research/published/White-Paper-on-the-Dialogues-on-Diversifying-Clinical-Trials-Conference.pdf [Accessed 22 June 2020].

- Use of visiting nurses, home health aides, phlebotomists and others to enable clinical trial activities in participant's home and/or at times and convenient locations for the participants.
- Utilize mobile technologies, including telemedicine, mobile devices, email, internet portals, etc., and real-time data capture to allow access to or submission of information during trial conduct.
- Note that access to electronic platforms are more challenging in certain communities. Access to digital technology and internet among low-income, rural, disabled, and underrepresented minority communities differs from well-resourced communities.
- Recognize that not all participants are comfortable with having people visiting their home.

- If requested by the participant, provide a letter to the participant's workplace or employer to communicate the expectations of participation in the research study with careful attention to privacy and confidentiality.

SPONSORS/CROs

- Allocate study budget for retention activities

13.6 Payment

KEY SUMMARY

- The financial burden of participating in clinical trials can be significant and will impact individuals with differing financial capacity differently – those who are least able to afford the costs of clinical trial participation will also face the largest burden if there is no reimbursement or there are delays in repayment.
- Reimbursement – for reasonable, out-of-pocket expenses incurred by an individual during participation in a research study – is generally accepted as ethical and as a way to return a participant to their financial baseline prior to the study.
- Compensation – the reimbursement for time and burden of clinical trial participation – enables enrollment for those where a financial barrier is inhibiting their participation in research.
- Incentive payments to participants remain controversial; certain payments raise a concern of undue influence wherein *excessive* payment may lead to compromised decision-making.

The financial burden of participating in clinical trials[534] can be significant and will impact individuals with differing financial capacity differently. Financial hardship in clinical research, often unrecognized, emanates from a number of sources including routine costs, copayments, or deductibles; transportation, lodging, meals, child or elder care; lost wages (or lost vacation days); and the expenses of participant caregivers (e.g., parents, partners, etc.). Notably, those that are least able to afford the costs of clinical trial participation are also those individuals who will face difficulty with delays in repayment: immediate reimbursement or prepayment is preferable and is becoming standard practice for many research sites. Reimbursement of out-of-pocket expenses, and compensation for time and burden, is not considered undue

[534] For clarity, in this section we emphasize that we are referring to payments (reimbursement for expenses and compensation for time and burden) to research participants in a clinical trial, not payments to individuals involved in study design conversations or focus group interviews in advance of a trial nor to patient navigators or similar members of the public.

inducement to participate.[535, 536] The U.S. FDA has confirmed this interpretation,[537] as have other regulatory agencies.[538] The 2016 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Health-related Research Involving Humans states that, "Research participants should be reasonably reimbursed for costs directly incurred during the research, such as travel costs, and compensated reasonably for their inconvenience and time spent."[539] Participants should not be required to incur research expenses; reimbursement—and compensation—is concordant with the principle of justice and fair participant selection.

Despite regulatory guidance and ethical advice to the contrary, payment to participants has remained controversial. Only certain payments raise a concern of undue influence wherein excessive payment leads to compromised decision-making and engaging in activities that an individual would otherwise decline. [540,541] Reimbursement for research-related expenses,

[535] Largent EA, Fernandez Lynch H. Paying Research Participants: Regulatory Uncertainty, Conceptual Confusion, and a Path Forward. Yale J Health Policy Law Ethics. 2017;17(1):61–141.
[536] Gelinas L, Largent EA, Cohen IG, Kornetsky S, Bierer BE, Fernandez Lynch H. A framework for ethical payment to research participants. New Engl J Med. 2018; 378:766-771. DOI: 10.1056/NEJMsb1710591
[537] U.S. FDA. Payment and reimbursement to research subjects. Guidance to Institutional Review Boards and Clinical Investigators. January 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects [Accessed 22 June 2020].
[538] U.S. Office of Human Research protections. U.S. Dep't of Health & Human Servs., *When does compensating subjects undermine informed consent or parental permission?* https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/# [Accessed 22 June 2020].
[539] Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Health-Related Research Involving Humans. 2016;44. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf [Accessed 22 June 2020].
[540] Gelinas L, Largent EA, Cohen IG, Kornetsky S, Bierer BE, Fernandez Lynch H. A framework for ethical payment to research participants. N Engl J Med 2018: 387: 766-771.
[541] HHS OHRP SACHRP Recommendations. September 30, 2019 Letter to the HHS Secretary. Attachment A-Addressing Ehtical Concerns Offers of Payment to Research Participants. https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-september-30-2019/index.html [Accessed 22 June 2020].

Figure 41: Potential reimbursable expenses incurred by research participants

- Transportation
  - Train, bus, or air expenses
  - Mileage per standard national rates
  - Taxi, Uber, or Lyft expenses
  - Car rental expenses, if allowed
- Parking
  - Hotel, AirBnB or equivalent (maximal rate adjusted for location)
  - Food
- Breakfast, lunch, dinner
- Incidentals
  - Childcare expenses
  - Ancillary medical expenses incurred as a consequence of research participation
  - Costs of medical insurance, if required
  - Additional individual or family expenses
  - Other out-of-pocket expenses

broadly interpreted (see Figure 41), and for time and burden of participation (here termed compensation) has been generally endorsed. Optimally a participant should not be left "worse off" financially for participating in research, although fair payment is not mandatory and many studies proceed in the absence of compensation when budgets are insufficient. If compensation for time or burden is considered, all participants in a similar geographic location should be compensated similarly, at a fair payment for the locality. Guidance and insight on fair-market compensation from a Community Advisory Board could help alleviate concerns of both IRBs and potential participants. Similarly, reasonable tokens of appreciation (small payments or gifts of thanks), particularly appropriate in pediatric studies or when the study budget does not allow reimbursement for expenses, should be permitted.

Notably, in all interventional research, an IRB or ethics committee will review a protocol—in the absence of considerations of payment—to ensure clinical equipoise, that risks are minimized, and that the potential benefits match or exceed the risks. The amount and schedule of payments are considered by the review committee only after the protocol is deemed approvable. These safeguards should be coupled with methods to ensure participant

understanding (e.g., teach-back, wherein a participant explains what they have understood to the study team member).[542]

Importantly, the ability to reimburse and compensate individuals for expenses, time, effort, and burdens of research will help individuals who might otherwise not be able to participate. These include economically disadvantaged individuals or their caregivers[543] who might not be able to afford the expenses of participation. It is important for financial issues, both payments and expenses (including co-pays if necessary) be clear in the screening and informed consent process. Only with clarity can a potential participant make an informed choice.

[542] See for instance, Interactive Techniques - MRCT Center Health Literacy in Clinical Research. Available at: https://mrctcenter.org/health-literacy/tools/overview/interactive-techniques/#teachback [Accessed 22 June 2020].
[543] Gelinas L, White SA, Bierer BE. Economic vulnerability and payment for research participation. Clinical Trials. 2020 Feb 17:174077452090559

RECOMMENDATIONS

INVESTIGATORS / SITES

- Clarify routine costs, co-payments, deductibles, and other potential financial burdens.
- Present in the informed consent document information concerning:
  - Expenses that the participant will be expected to incur and that will not be reimbursed.
  - Payment that the participant is expected to receive (i.e., reimbursement, compensation, and incentive payments), including tax-reporting responsibilities, if applicable.
- Reimburse expenses of attendant for certain individuals (e.g., children or older individuals or individuals with physical, mental, or intellectual disabilities) that may require company or an attendant (e.g., participant partners, care givers, family, guardians) to attend clinical trial visits or research procedure.

INVESTIGATORS / SITES, IRBs

- Present planned payment schedule and methods to IRB/REC for review and approval

SPONSORS / CROs, INVESTIGATORS / SITES

- Realize that, while payment for individual participants should be equal, payment amounts may differ by region, country, or location depending upon purchasing power or the average working wage.
- Streamline prior authorization for expenses and, if possible, provide prepayment for expenses.
- Do not tie payment for research-related expenses to completion of the trial but rather to expenses incurred and time and effort expended.
- Consider completion bonuses, while potentially justifiable, separately from reimbursement or compensation.
- Provide financial resources as available and financial counselors if necessary.

14. The Role and Responsibility of the IRB/REC in Inclusion and Equity

KEY SUMMARY

- The IRB/REC is focused on protections of human participants, including vulnerable populations. A principal tenet of ethical review and approval of clinical research is justice, the fair selection of participants.
- The IRB/REC is a central and controlling locus to review considerations of and promote diversity and inclusion in clinical research.
- One role of the IRB/REC is the routine and systematic review of methods to ensure inclusion of diverse populations, optimally buttressed by appropriate policies and procedures.
- The IRB/REC should review each clinical research protocol and application, including the study protocol, eligibility criteria, informed consent form, questionnaires/surveys, information sheets, and other documents for inclusion, across all relevant dimensions of diversity.
- The IRB/REC can assign or appoint one (or more) IRB/REC panel member(s) to be responsible for the initial review of the clinical trial application to ensure it promotes recruitment, enrollment, and retention of a diverse participant population.

IRBs/RECs provide an important control in the conduct of human clinical trials; across the globe, almost no clinical trial may proceed until the written protocol and informed consent document is reviewed and approved by an IRB/REC. The authority of IRBs/RECs is well-appreciated by investigators, institutions, and sponsors alike: while an organization may decline to initiate a clinical research protocol, in the U.S. and elsewhere, the research cannot proceed in the absence of IRB/REC approval. This control positions the IRB/REC as a central locus to review considerations of diversity and inclusion in clinical research, and that function is consistent with the ethical obligations of the IRB/REC. The IRB/REC committee is charged with ensuring not only that risks and burdens are minimized, that risks are balanced by potential benefit, but also that justice and respect for persons are considered. And by justice, it is the equitable selection

of participants in research, and as the Belmont Report[544] opines, "at two levels: the social and the individual." Further, the Belmont Report[545] states:

> Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

The commitment to justice has—largely for historical reasons—been understood as protection of participants from the potential harms of research (see Section 2.2 "Justice and equity in health care research"). The application of justice, however, explicitly embodies a responsibility to *include* subgroups who have been understudied or underserved to participate in research such that they have access to the benefits of the knowledge gained by the research as a population as well as equal opportunity to the potential direct benefits of the research. Similarly, the concept of fairness as *access to the benefits* of research has implications for subgroups who have been understudied, whether systematically or incidentally, and is at the core of current concerns about diversity in clinical trials.

While these committees are optimally positioned to promote inclusion, currently IRBs/RECs and their institutional and organizational leaders may not uniformly embrace or execute this responsibility. As IRBs/RECs assume greater oversight of fair inclusion of diverse populations, the appropriate selection of multi-cultural IRB/REC members to represent the communities that

[544] U.S. Department of Health and Human Services. Office of the Secretary. The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Available at: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html#xjust. [Accessed 22 June 2020].

[545] Similar principles are embodied in other documents such as the World Medical Association's Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/), the Council for International Organizations of Medical Sciences (CIOMS, https://cioms.ch) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH, https://www.ich.org) guidelines. [Accessed 22 June 2020].

they serve and/or for whom they provide oversight should be considered. Implicit bias and cultural competence training of IRB/REC members and staff of the human research protections offices may help sensitize the members and staff to their own competencies in this regard. Finally, leadership should encourage and empower intervention whenever inappropriate exclusion is evident, independent of whether the IRB/REC has, in its past, been proactive in this regard. In addition to the membership and position of the IRB/REC, a number of actions can be considered to provide oversight for diversity and inclusion (Figure 42), and these are further enumerated below.

Figure 42: Oversight of diversity and inclusion during ethics review

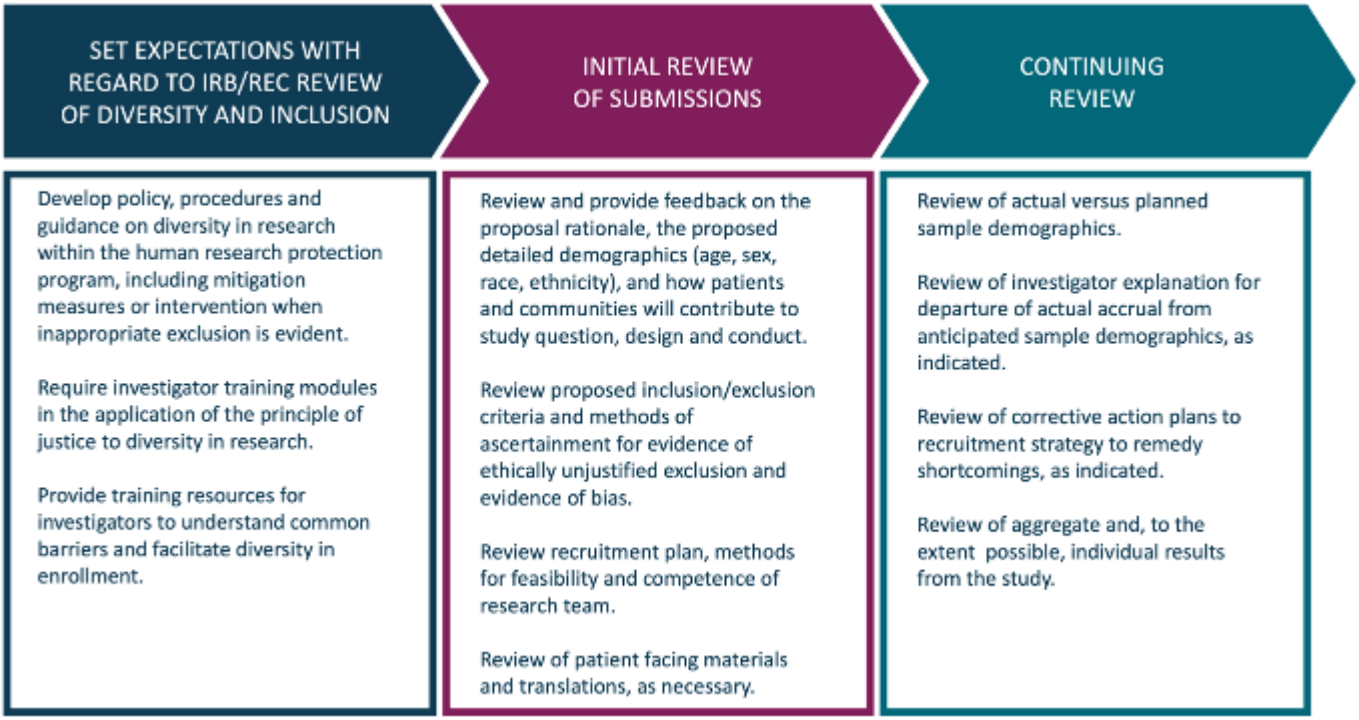


Figure 42 summarizes approaches related to diversity and inclusion that IRBs can use to increase the oversight and promote inclusion during the ethics review process.

14.1 Participant selection

At the time of initial review, an investigator (or sponsor) should be expected to provide, and the IRB to examine, the demographic characteristics of the proposed study sample. Importantly, the investigator (or sponsor) should be asked to provide a scientific and ethical justification if the proposed sample reflects a significant departure from the demographics of the condition being studied, for example, with respect to age, sex, race, and ethnicity. At the time of continuing review, when the accrued sample demographics deviate significantly from those proposed initially, the IRB should seek explanation, and where necessary, determine whether alternative or additional recruitment strategies are warranted.

14.2 Inclusion/exclusion and eligibility criteria

Efforts to broaden eligibility criteria permit enrollment of subgroups that have historically been excluded to minimize risk (see Section 13.3 "Eligibility criteria"). For example, the routine exclusion of individuals with comorbid conditions functions to protect participants from risk but limits the generalizability of study findings. As an additional example, recent regulatory guidance related to research on suicide[546] underscores the scientific shortcomings associated with the blanket exclusion of individuals at risk for suicide in drug development for conditions in which suicide is common. Minimizing short term risk associated with study participation must be balanced with the long-term problem of bringing to market a depression drug that has not been tested in individuals at risk for suicide.

14.3 IRB/REC policies and procedures to support inclusion

The IRB/REC should have policies and procedures that systematize regular review of protocols for inclusion in the:

(1) Protocol submission application, requiring a statement on patient and community input to study question, study design, and study conduct;

[546] The National Institute of Mental Health: https://www.nimh.nih.gov/funding/clinical-research/conducting-research-with-participants-at-elevated-risk-for-suicide-considerations-for-researchers.shtml [Accessed 22 June 2020].

(2) Requirement of justification for eligibility criteria, with particular attention to any population that may be excluded from participation (e.g., age greater than 65 years old, women of child-bearing age, non-native English speakers);
(3) Review of the demographics of the intended population to be enrolled to mirror the population using, or likely to utilize, the intervention;
(4) Review of the recruitment and feasibility plan;
(5) Review of study conduct procedures to maximize flexibilities;
(6) Review of demographic breakdown of enrolled populations at continuing review, and as required and necessary, corrective action plans for deviations from plan;
(7) Review of patient-facing materials for health literacy principles (e.g., plain language, numeracy, design, visualization), including whether materials have undergone user testing;
(8) Review of potentially necessary translation of patient materials, and consideration of back translation as necessary
(9) Consideration for payments for participants and caregivers (i.e., reimbursement, compensation and/or incentive) is appropriate and whether adequate provisions to ensure participant confidentiality and privacy are in place; and
(10) Review of return of aggregate and, to the extent possible, individual results from the study.

14.4 Assigning the responsibility for monitoring for diversity

These are challenging expectations for any IRB/REC. One suggestion is for the chair of the IRB/REC to assign one (or more) IRB/REC member(s) the responsibility of reviewing the clinical research application, including the protocol, informed consent, questionnaires/surveys, information sheets, and other documents for inclusion in recruitment, enrollment, and retention, and across all relevant dimensions of diversity. That would include evidence of patient, participant, public and/or community involvement (and its diverse representativeness), eligibility criteria, study conduct accommodations, payment options, recruitment plan, health literate documents, etc., at least until these considerations are assumed more generally by the members and become standard in the work of the IRB/REC. If protocols and study documents are reviewed by IRB/REC administrators in advance of review by the full board, these considerations could also be part of routine checklists that are used.

14.5 Educational resources for the investigator and study team

The IRB/REC is often positioned as and considered a resource to the investigator and the study team in terms of participant interactions. Insofar as possible, the IRB/REC should provide educational materials for the investigator community and their research teams. These resources may include:

- Guidance on implicit bias and cultural competence training
- Guidance on preparing health literate materials, including informed consent documents, recruitment advertisements, participant information sheets, plain language summaries of the trial, and language to explain return of individual results obtained during a trial
- Explanations and examples of respectful "teach back" conversations, a method to ensure participant understanding of a conversation or printed document
- Resources to clarify when translation is necessary, when back translation is appropriate, and how to conduct conversations through a translator
- Examples of successful recruitment strategies to consider
- Model recruitment strategy document, with completed examples reflecting different subgroup populations and how the strategy may be individualized
- Checklists for permissible study conduct flexibilities, including accommodations that may be provided to allow broad participation
- Procedures for estimating payment for participants, with allowable estimates of payments for research procedures in the geographic location, estimates for time and burden depending on the study, and provisions for payment methods, including tax implications if any.

RECOMMENDATIONS

- Ensure the IRB/REC is composed of a diverse group of individuals, optimally representing local underserved and minority communities.
- Provide training to IRB/REC members and administrators on implicit bias and cultural competence to underrepresented and underserved populations. Additional recommendations can be found in Chapter 10 "Workforce and Diversity: Training and Development."
- Require investigators to provide demographic characteristics of the proposed study sample as well as a feasibility plan based on the local community at the time of initial IRB review.
- Review summary of overall trial plan and site(s)-specific plans based on epidemiology of disease and intended use population.
- At continuing review, require investigators to provide metrics of the demographics of participants enrolled to date. Examine enrollment demographic characteristics compared to plan. Seek explanation from investigators if the demographic characteristics proposed at the beginning of the study deviate from the actual enrollment. Request remediation plan if enrollment deviates from plan significantly.
- Designate a member of the IRB/REC to act as a "patient representative," responsible for ensuring:
    - Process for patient, public, and community input in development of study question, study design, and study conduct was adequate and submitted protocol represents their input.
    - Review of study conduct parameters for flexibilities.
    - Review of eligibility criteria to be as inclusive as possible and as restrictive as necessary. Review justification for any ineligibility criteria.
    - Underserved populations are represented in the research.
    - Informed consent document and other participant-facing materials are health literate for the intended population and have undergone user testing by relevant populations.
    - Documents are translated and images are culturally appropriate.

  - Participants will be provided aggregate and, to the extent possible, individual study results.
  - Community will be provided results in a format useful to them.
- Revise policies, standard operating procedures, investigator and IRB staff human participant education requirements, and tools and checklists so that they incorporate review and oversight of diversity and inclusion in research at initial and continuing review.
- Develop an index of recruitment and retention strategies unique to the institution and its specific study populations.
- Provide a prototype recruitment and retention strategy document for investigators to emulate.
- Create and share model tracking and monitoring tool for enrollment and retention (particularly for tunderrepresented and underserved populations) with investigators.

15. Special Populations

The MRCT Center workgroup acknowledges that diverse populations have different issues to consider in order to optimize their participation in clinical research. Throughout this guidance, we have examined challenges and strategies to increase research participation by these diverse populations. We recognize that many underrepresented groups, communities and subpopulations are especially "hard to reach," or require additional considerations, ethical and practical, in order to improve their engagement, recruitment and participation. We use the term "special populations" to denote such individuals and groups.

We have reserved this chapter for future work and intend to develop content to stimulate understanding, advance preparedness, and facilitate the inclusion of special populations in research. The work will include guidance, points to consider, and educational tools.

We intend to include the following:

- Age-related considerations
- Racial/ethnic and religious groups
- Individuals with disabilities
- Additional special populations, including but not limited to
    - Women of child-bearing age, or those who are pregnant or lactating
    - Individuals who have limited literacy or limited primary language proficiency
    - The uninsured and underinsured

Transition from Parts C to E to Part F

The goal of Part F of this Guidance Document is to prepare and align for the future. It considers the role of genetics in clinical research and personalized medicine, the roles and responsibilities of stakeholders involved in clinical research, and how we, as a clinical research community, move forward. This Part builds upon the earlier parts of this Guidance Document in which we have considered theoretical arguments for the inclusion of diverse populations in research and highlighted regulatory and ethical guidance (Part A and B), and considered the practical barriers that prevent, and potential recommendations and approaches to promote, routine participation of underrepresented, underserved, and diverse populations (Parts C through E).

Part F – Stakeholder Commitments and the Future

We begin Part F by considering **the role of genetics** in disease and in treatment response as well as how improved genetic testing and ancestral representation in genomic databases may have an impact on clinical research (Chapter 16). In Chapter 17 "**Stakeholder Roles, Responsibilities and Accountability in Promoting Diversity"** we consider diverse representation and inclusion in clinical research as a shared responsibility by all in the research enterprise. We specifically describe practical examples of potential actions each stakeholder could take to promote diversity. The last chapter of this Guidance Document, Chapter 18 "**Future Considerations and Conclusions,"** sets forth what we collectively need to do, as a research community, to achieve meaningful diverse inclusion in research.

16. Genetics and Clinical Research Diversity: Implications of Recent Advances in Genetics and Genomics

Differences in disease burden and responses to medical therapies across racial and ethnic groups have been well documented.[547] According to a review by the FDA, approximately 20% of newly approved molecular entities (NMEs) indicated differences in exposure and/or response across racial or ethnic groups that resulted in different prescribing recommendations for specific populations.[548] In Section 2.3 "Defining diversity," we recognize that the underlying basis for observed subpopulation differences are often unclear and may be due to intrinsic and/or extrinsic factors, including social, environmental and behavioral determinates, and/or genetic background. This chapter introduces how genetics and genomics can influence disease and treatment response, how inclusivity in genomic databases may improve health equity through understanding, and how the growth of direct-to-consumer genetic testing—and attention to ancestral diversity in the research specimens used in research and deposited in repositories—may impact understanding of pathophysiology, disease manifestations, and heterogeneity of treatment outcomes.

Recent advances in genetics, genomics,[549] genomic technology, and low-cost genomic screening have heralded an era of great promise for precision medicine and population health—and the possibility that disease prevention and treatment can be individually tailored.[550] This is the foundation behind the concept of "personalized medicine." Genetics and genomics provide important, scientifically objective tools that may define populations at risk and predict

[547] Walsh R, Goh BC. Population diversity in oncology drug responses and implications to drug development. Chinese clinical oncology. 2019 Jun;8(3):24.
[548] Ramamoorthy A, Pacanowski MA, Bull J, Zhang L. Racial/ethnic differences in drug disposition and response: review of recently approved drugs. Clinical Pharmacology & Therapeutics. 2015 Mar;97(3):263-73.
[549] According to the World Health Organization, genetics is the study of heredity and genomics is the study of genes, their functions and related inter-relationships. The fields of genetics and genomics have a unique vernacular, different from the majority of this Guidance Document, that is specific to the scientific study of genes and alleles, their functions and their interactions. *Reference*: World Health Organization. Human Genomics in Global Health [Internet]. Available: https://www.who.int/genomics/geneticsVSgenomics/en/ [Accessed 22 June 2020]
[550] Shah RR, Gaedigk A. Precision medicine: does ethnicity information complement genotype-based prescribing decisions?. Therapeutic advances in drug safety. 2018 Jan;9(1):45-62.

responses to specific treatments.[551] For example, self-identification as Black correlates with a higher frequency of PCSK9[552] gene variants associated with lower levels of low-density lipoprotein (LDL) and reduced risk of coronary heart disease (see "Case Study: PCSK9" in *Toolkit*).[553,554] Earlier (see Chapter 2 " The Case for Diversity in Clinical Research") we discussed that race, ethnicity, and other demographic variables may be used as imperfect and flawed surrogates of potential biological differences (in addition to their importance in the health equity domain). Analysis of genomics medicine may enrich or supplant the use of race, ethnicity, and other surrogate biological markers, and lead to improved application of personalized medicine.

16.1 Geographic and genetic ancestry

Geographic ancestry, a means of describing family origins from geographic locations, and genetic ancestry, a way of quantifying a person's ancestral background statistically by understanding the history of a genome, are enabling researchers to have a broader understanding of disease differences, and paving the path towards precision medicine. For example, different segments of a genome (the genetic material of an organism) can have their own ancestral history that trace to

Figure 43: Latinas and reduced incidence of breast cancer

Breast cancer incidence is highly variable across different racial and ethnic groups in the United States; age adjusted incidence found women of Latin American origin have a lower rate than those of European American or African American descent (i.e., 90.8 versus 133.4 and 121.4 per 100,000). Within the Latina population, women with a higher proportion of Indigenous American ancestry are at a lower risk of developing breast cancer. The incidence findings prompted breast cancer genome-wide association studies (GWAS) in Latinas that identified a variant at the 6q25 locus as a protective risk variant for reduced incidence of breast cancer.

[551] Centers for Disease Control and Prevention. Tier 1 Genomics Applications and their Importance to Public Health [Internet]. Office of Science, Office of Genomics and Precision Public Health. March 6, 2014; cited 24 March 2020. Available: https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm

[552] PCSK9 (Proprotein convertase subtilisin/kexin type 9) is a gene that encodes a protein that regulates the receptors for low density lipoproteins (LDL) in the blood. High levels of LDL are associated with coronary heart disease.

[553] Cohen JC, Boerwinkle E, Mosley Jr TH, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. New England Journal of Medicine. 2006 Mar 23;354(12):1264-72.

[554] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS. Evolocumab and clinical outcomes in patients with cardiovascular disease. New England Journal of Medicine. 2017 May 4;376(18):1713-22.

Figure 44: Genotyping for CYP2C19 and clopidogrel

Clopidogrel is an anti-platelet drug that is used to reduce the risk of heart disease, heart attacks, and stroke. For it to work, the drug must be converted to an active form by enzymes in the body called cytochrome 450 (collectively referred to as CYP enzymes). Populations of Asian ancestry are less responsive to clopidogrel, a finding that has been shown to be due to an increased frequency of the gene CYP2C19 loss-of-function (LOF) alleles that impairs the conversion of clopidogrel into its active form and therefore reduces its clinical effectiveness.

Characterizing the CYP2C19 gene (termed genotyping) can be used in clinical care to guide selection of alternate antiplatelet therapy where CYP2C19 genetic variations do not alter effectiveness. Approximately 3–5% of European, 24% of Japanese, 15% of Koreans and 9% of Chinese populations are "poor metabolizers," have no CYP2C19 function and require alternate antiplatelet therapy. Genotyping also helps guide dosage needed, since variation in the CYP2C19 gene can alter metabolism in some individuals such that higher or lower dosages are needed. Nearly 28% of South Asians are more likely to have genetic polymorphisms that result in rapid metabolism and potentially higher bleeding risk.

different populations (see Figure 43 "Latinas and reduced incidence of breast cancer";[555] Figure 44 "Genotyping for CYPC19 and clopidogrel;"[556,557,558] and "Case Study: Clopidogrel (Plavix®)" in *Toolkit*).

[555] Fejerman L, Ahmadiyeh N, Hu D, Huntsman S, Beckman KB, Caswell JL, Tsung K, John EM, Torres-Mejia G, Carvajal-Carmona L, Echeverry MM. Genome-wide association study of breast cancer in Latinas identifies novel protective variants on 6q25. Nature communications. 2014 Oct 20;5:5260.
[556] Royal CD, Novembre J, Fullerton SM, Goldstein DB, Long JC, Bamshad MJ, Clark AG. Inferring genetic ancestry: opportunities, challenges, and implications. The American Journal of Human Genetics. 2010 May 14;86(5):661-73.
[557] Hasan MS, Basri HB, Hin LP, Stanslas J. Genetic polymorphisms and drug interactions leading to clopidogrel resistance: why the Asian population requires special attention. International Journal of Neuroscience. 2013 Jan 16;123(3):143-54.
[558] Johnson JA, Roden DM, Lesko LJ, Ashley E, Klein TE, Shuldiner AR. Clopidogrel: a case for indication-specific pharmacogenetics. Clinical Pharmacology & Therapeutics. 2012 May;91(5):774-6.

Geographic ancestry may correlate with differences in responses to various medical treatments. While the mechanism of these differences are often unknown, they may, in some cases, be a clue to genetic differences. For example:

- Self-defined geographic African ancestry is a strong predictor of hypertension risk, increased treatment responsiveness (e.g., diuretics, calcium channel blockers), or decreased responsiveness to anti-hypertensive therapies (e.g., ACE inhibitors). While available data are inconclusive as to the mechanisms of differences, some have hypothesized genetically determined predisposition to salt and water retention and suppressed plasma renin activity.[559]

- Several adverse drug reactions (i.e., the serious skin and mucosal disorder known as Stevens-Johnson Syndrome caused by the anti-seizure medication carbamazepine) have been shown to have significant associations with specific alleles of human leukocyte antigen (HLA) genes. Most of the HLA-associated adverse drug reactions have demonstrated ethnic specificity, due likely to the frequency in differences of the alleles between populations.[560]

[559] Brewster LM, Seedat YK. Why do hypertensive patients of African ancestry respond better to calciumblockers and diuretics than to ACE inhibitors and β-adrenergic blockers? Asystematic review. BMC medicine. 2013 Dec 1;11(1):141.
[560] Fan WL, Shiao MS, Hui RC, Su SC, Wang CW, Chang YC, Chung WH. HLA association with drug-induced adverse reactions. Journal of immunology research. 2017;2017.

16.2 Genomics and health equity

Figure 45: PCSK9 gene – identified as important for low-density lipoprotein cholesterol (LDL-C) lowering

In a bi-racial cohort, self-identified Blacks had a higher frequency (2%) compared to Whites (<0.1%) of two of the three common PCSK9 gene loss-of-function (LOF) variants, lower LDL-C, and decreased cardiovascular disease (CVD) risk. Identification of genetic variants and enriched polymorphisms proved important in the discovery and development of PCSK9 inhibitors; to date more than 20 functional LOF PCSK9 variants have been reported. Discovery of these variants was a result of initial studies conducted in bi-racial cohorts and provides an example of how diversity of participants can contribute to discovery research.

Racial and ethnic categories in the U.S. are viewed primarily as social constructs and do not represent genetically distinct or homogenous entities. However, as noted above, self-identified race is at times a useful surrogate marker of genetic variation that may have implications for both disease prevalence and drug response (see Figure 45 "PCSK9 gene" and "Case Study: PCSK9" in *Toolkit*).[561,562] While genomics has the potential to improve health outcomes broadly, there is also the potential peril that benefits may not be equitably available to all populations.[563] That is because, thus far, most genomic and genetic research has used DNA collected from descendants of Europeans,[564] meaning that the related medical applications and disease risk assessments are likely to predominantly benefit those populations. Racial and ethnic minorities are underrepresented in genomic databases, and this can be particularly impactful in oncology care where treatment decisions are often made based on genotyping of the cancer.[565] The lack of diversity limits our understanding of how genetic variants affect disease across populations since the results obtained in one population may not be transferable to another population of different ancestry (see Figure 46 "Triple negative

[561] Folsom AR, Peacock JM, Boerwinkle E, Atherosclerosis Risk in Communities (ARIC) Study Investigators. Variation in PCSK9, low LDL cholesterol, and risk of peripheral arterial disease. Atherosclerosis. 2009 Jan 1;202(1):211-5.
[562] Kent ST, Rosenson RS, Avery CL, Chen YD, Correa A, Cummings SR, Cupples LA, Cushman M, Evans DS, Gudnason V, Harris TB. PCSK9 loss-of-function variants, low-density lipoprotein cholesterol, and risk of coronary heart disease and stroke: data from 9 studies of blacks and whites. Circulation: Cardiovascular Genetics. 2017 Aug;10(4):e001632.
[563] Bustamante CD, Francisco M, Burchard EG. Genomics for the world. Nature. 2011 Jul;475(7355):163-5.
[564] Gurdasani D, Barroso I, Zeggini E, Sandhu MS. Genomics of disease risk in globally diverse populations. Nature Reviews Genetics. 2019 Sep;20(9):520-35.
[565]Spratt DE, Chan T, Waldron L, Speers C, Feng FY, Ogunwobi OO, Osborne JR. Racial/ethnic disparities in genomic sequencing. JAMA oncology. 2016 Aug 1;2(8):1070-4.

Figure 46: Triple negative breast cancer

Breast cancer is the second most common cancer and a leading cause of cancer-related mortality for women in the U.S. Breast cancer can be subclassified on the basis of three molecular markers; estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (EGFR2/Her2) – whose presence or absence correlate with prognosis and guide the choice of therapeutic interventions. Triple negative breast cancer (TNBC) is an aggressive type of breast cancer comprising 15-20% of all breast cancers. While some breast cancers may test positive for ER, PR or EGFR2/Her2, TNBC tests negative for all three and therefore does not respond to the therapies that target these proteins, making it difficult to treat. TNBC is more common in women of African ancestry compared to other ethnic groups and is associated with worse outcomes. Although not yet elucidated, contributory factors to the observed disparity in outcome between women of African and European ancestry may include the interplay of genetic, biological and socio-economic factors, access to screening and standard treatment, culture and environment. Adequate representation of racial and ethnic minorities in genomic databases could help explain the increased prevalence of TNBC in women of African ancestry and is a particularly important unmet research need.

breast cancer").[566,567] Significant gaps in knowledge exist in genomic medicine and there is an opportunity for further research to enhance the knowledge base for precision health.[568]

Existing health disparities and the impact of underrepresentation in clinical research may be exacerbated if the implementation of genomic medicine does not intentionally address diversity and health equity. The lack of diversity in genomic research affects understanding the relationships of genes and disease in unstudied and understudied populations.[569] Genomic databases need greater inclusion of diverse

[566] Wojcik GL, Graff M, Nishimura KK, Tao R, Haessler J, Gignoux CR, Highland HM, Patel YM, Sorokin EP, Avery CL, Belbin GM. Genetic analyses of diverse populations improves discovery for complex traits. Nature. 2019 Jun;570(7762):514-8.
[567] Siddharth S, Sharma D. Racial disparity and triple-negative breast cancer in African-American women: a multifaceted affair between obesity, biology, and socioeconomic determinants. Cancers. 2018 Dec;10(12):514.
[568] Jooma S, Hahn MJ, Hindorff LA, Bonham VL. Defining and Achieving Health Equity in Genomic Medicine. *Ethnicity & disease*. 2019;*29*(Suppl 1): 173-178.
[569] Landry LG, Ali N, Williams DR, Rehm HL, Bonham VL. Lack of diversity in genomic databases is a barrier to translating precision medicine research into practice. Health Affairs. 2018 May 1;37(5):780-5.

populations and ancestral information. Table 16 summarizes how geographic or ethnic ancestry can be associated with different responses to treatment or diseases. Strategies to improve research diversity and health equity should include addressing underrepresentation of diverse populations in genomic preclinical, clinical, and public health research. Further examples below show how genomics may influence diagnosis and treatment in oncology (Section 16.2.1 "Oncology, genomics and ethnicity") and hepatitis (Section 16.5.2 "Hepatitis C, genomics, geographic region, ethnicity").

Table 16: Examples of differences in treatment response based on race, ethnicity, geographic ancestry, and genomics

CONDITION AND/OR TREATMENT	GEOGRAPHIC/ ETHNIC ANCESTRY	SUMMARY
BiDil (ISDN/Hydralazine) for treatment of heart failure[570]	African Americans, self-identified	There are strong benefits of the drug in self-identified Blacks with heart failure. The explanation for this remains unknown.
ACE Inhibitors for treatment of hypertension[571]	African Ancestry	Individuals of African ancestry are at greater risk for hypertension and have historically been less responsive to standard treatments through angiotensin-converting enzyme (ACE) inhibitors. Self-reported Blacks are also at greater risk for angioedema when treated with ACE inhibitors, an effect for which the explanation remains unknown.
Clopidogrel	East Asians, Native Hawaiians	Genetic variation in expression of cytochrome (CYP) enzymes results in different treatment responses among individuals. Anti-platelet therapies can be less efficacious in

[570] Kahn J. Misreading race and genomics after BiDil. Nature Genetics. 2005 Jul;37(7):655-6.
[571] Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. American journal of hypertension. 2004 Feb 1;17(2):103-11.

for treatment of cardiovascular disease[572,573]		persons with CYP2C19*2 or CYP2C19*3 allele and there are higher frequencies of these genetic variations in East Asians, Native Hawaiians, other Pacific Islanders.
Carbamazepine for treatment of seizures[574]	Asians	Approximately 12% of people living along the border between Thailand and Malaysia have a genetic predisposition to the skin reaction called Stevens-Johnson Syndrome when given the anti-seizure drug carbamazepine. Recent data implicates the HLA allele B*1502 as a marker for carbamazepine-induced Stevens–Johnson Syndrome and toxic epidermal necrolysis in Han Chinese. This allele is seen in high frequency in many Asian populations other than Han Chinese, but there are few data on whether the allele is a marker for this severe outcome in anyone other than Han Chinese. The association has not been found in Caucasian patients. The FDA recommends genotyping all Asians for the allele.
PCSK9 Inhibitors	African Americans, self-identified	Self-identified Blacks are more likely to have two of the three common PCSK9 gene variants associated with loss-of-function (LOF), lower LDL and decreased CVD risk than Whites. See Figure 45 – PCSK9 gene.

[572] Royal CD, Novembre J, Fullerton SM, Goldstein DB, Long JC, Bamshad MJ, Clark AG. Inferring genetic ancestry: opportunities, challenges, and implications. The American Journal of Human Genetics. 2010 May 14;86(5):661-73.
[573] Hasan MS, Basri HB, Hin LP, Stanslas J. Genetic polymorphisms and drug interactions leading to clopidogrel resistance: why the Asian population requires special attention. International Journal of Neuroscience. 2013 Jan 16;123(3):143-54.
[574] Lim KS, Kwan P, Tan CT. Association of HLA-B* 1502 allele and carbamazepine-induced severe adverse cutaneous drug reaction among Asians, a review. Neurol Asia. 2008 Jun 1;13(6):15-21.

for treatment of high cholesterol[575,576]		
Sickle Cell trait and Disease[577]	Mediterranean and sub-Saharan African origin	Sickle cell trait is a disease that results from a mutation substituting thymine for adenine in the sixth codon of the beta-chain gene (CAG to GTG) causing coding of valine instead of glutamate in position 6 of the hemoglobin beta chain. Because this mutation is more common in individuals with African ancestry, it is frequently thought of as a disease that only affects those of African decent, though it is found in other ethnicities.
NASH (nonalcoholic steatohepatitis) and NAFLD (nonalcoholic fatty liver disease)[578]	Hispanics of Mexican, Dominican and Puerto Rican origin	Many Hispanics in U.S possess the PNPLA3 gene variation which has been associated with increased risk of NAFLD and NASH. Higher prevalence of NAFLD has been discovered in Hispanics of Mexican origin (33%) than in Hispanics of Dominican origin (16%; P<0.01) and Hispanics of Puerto Rican origin (18%; (P<0.01). Further studies needed to clarify differences in prevalence found among Hispanic subtypes living in the U.S.

[575] Folsom AR, Peacock JM, Boerwinkle E, Atherosclerosis Risk in Communities (ARIC) Study Investigators. Variation in PCSK9, low LDL cholesterol, and risk of peripheral arterial disease. Atherosclerosis. 2009 Jan 1;202(1):211-5.
[576] Kent ST, Rosenson RS, Avery CL, Chen YD, Correa A, Cummings SR, Cupples LA, Cushman M, Evans DS, Gudnason V, Harris TB. PCSK9 loss-of-function variants, low-density lipoprotein cholesterol, and risk of coronary heart disease and stroke: data from 9 studies of blacks and whites. Circulation: Cardiovascular Genetics. 2017 Aug;10(4):e001632.
[577] Steinberg MH, Sebastiani P. Genetic modifiers of sickle cell disease. American journal of hematology. 2012 Aug;87(8):795-803.
[578] Fleischman MW, Budoff M, Zeb I, Li D, Foster T. NAFLD prevalence differs among hispanic subgroups: the Multi-Ethnic Study of Atherosclerosis. World Journal of Gastroenterology: WJG. 2014 May 7;20(17):4987.

Cystic fibrosis[579]	Northern European Origin	Cystic fibrosis (CF) is a genetic disorder that affects mostly the lungs, but also the pancreas, liver, kidneys, and intestine. It is caused by the presence of mutations in both copies of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CF is most common among people of Northern European ancestry, affecting about one out of every 3,000 newborns (about one in 25 people is a carrier). It is least common in Africans and Asians.

[579] Estivill X, Bancells C, Ramos C. Geographic distribution and regional origin of 272 cystic fibrosis mutations in European populations. Human mutation. 1997;10(2):135-54.

16.2.1 Oncology, genomics and ethnicity

Genomics is increasingly important to advancing our understanding of cancer (as well as other diseases) and to the development of targeted therapies. For example, inherited mutations in the breast cancer genes (BRCA1 and BRCA2, see Figure 47) are associated with hereditary breast and ovarian cancer syndromes, an increased lifetime risk of breast and ovarian cancers, as well as association with several other cancers, including pancreatic and prostate cancers, and male breast cancer. [580]

Figure 47: BRCA genes mutations

> *"If you're an Ashkenazi Jewish woman like me, you may be at higher risk for breast cancer before 45."*
>
> -*Cara*, age 30

While everyone has BRCA1 and BRCA2 genes, some people are more likely to have mutations – for example, 1 in 40 Ashkenazi Jewish women have a BRCA gene mutation and are at a higher risk, at a younger age, for breast cancer.

Some cancers that do not appear to be caused by inherited genetic mutations may appear to run in families or disproportionately impact some population groups, perhaps the result of shared environments or lifestyles or perhaps the presence of a currently uncharacterized hereditary cancer syndrome. In the era of advances in "personalized medicine," if we are to provide the benefits of advances to all population groups and individuals, research across all groups is foundational for the improved understanding of the disease and the development of appropriate, targeted therapies.[581,582]

[580] Division of Cancer Prevention and Control, Centers for Disease Control and Prevention. Jewish Women and BRCA Gene Mutations [Internet]. April 5, 2019. Available online: https://www.cdc.gov/cancer/breast/young_women/bringyourbrave/hereditary_breast_cancer/jewish_women_brca.htm [Accessed 22 June 2020].
[581] Siddharth S, Sharma D. Racial disparity and triple-negative breast cancer in African-American women: a multifaceted affair between obesity, biology, and socioeconomic determinants. Cancers. 2018 Dec;10(12):514.
[582] Spratt DE, Chan T, Waldron L, Speers C, Feng FY, Ogunwobi OO, Osborne JR. Racial/ethnic disparities in genomic sequencing. JAMA oncology. 2016 Aug 1;2(8):1070-4.

16.2.2 Hepatitis C, genomics, geographic region, ethnicity

The Hepatitis C Virus (HCV) infection is a key example of the importance of the interaction between viral genomics and host genomics in the identification and development of appropriate "personalized" treatment.

Hepatitis C Virus infections have continued to increase in the U.S. since 2010[583] despite the availability of effective, curative therapy. There are six known major genotypes of the HCV that infect the liver that vary in prevalence (regional and ethnic/racial), disease severity, and response to treatment. Genotype 1 is the most common in the U.S. and is more common in Blacks than in others. Genotype 4 is most prevalent in the Middle East and Africa; genotype 5 most prevalent in South Africa; and genotype 6 most prevalent in Southeast Asia.[584] Hepatitis C is potentially curable; treatment efficacy must be tested and demonstrated for each of the major viral genotypes – thus tested in the populations and regions where these are prevalent.

16.3 Direct-to-Consumer genetic testing

As the cost of next-generation sequencing continue to decline, personal genomics will likely increasingly become a part of routine health care. Direct-to-Consumer genetic ancestry testing has become popular during recent years and, currently, the two major testing companies report approximately 25 million customers (AncestryDNA: 16+ million[585] and 23andMe: 12+ million[586]). Although there are limitations (e.g., different comparator databases), these companies have accumulated large databases that link genetics to geographic ancestry. These databases may help support our understanding of the relationship between genetics, geography, and ethnicity as well as potentially provide additional insights into the complex interactions between

[583] Centers for Disease Control and Prevention. Viral Hepatitis Surveillance—United States, 2017 [Internet]. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2019. Available at: https://www.cdc.gov/hepatitis/statistics/2017surveillance/pdfs/2017HepSurveillanceRpt.pdf
[584] Emmanuel B, Shardell MD, Tracy L, Kottilil S, El-Kamary SS. Racial disparity in all-cause mortality among hepatitis C virus-infected individuals in a general U.S. population, NHANES III. Journal of viral hepatitis. 2017 May;24(5):380-8
[585] Ancestry. Ancestry Company Facts [Internet]. Available at: https://www.ancestry.com/corporate/about-ancestry/company-facts [Accessed 22 June 2020]
[586] 23andMe. 23andMe Company About Us [Internet]. Available at: https://mediacenter.23andme.com/company/about-us/ [Accessed 22 June 2020]

biological and social determinants of health. However data analysis must account for the possibility (and likelihood) that genetics and social determinants of health are not independent variables, and thus any associations or conclusions may be biased; association of one is difficult to distangle from the other.[587] Indeed, genetic ancestry testing companies and biopharmaceutical companies are partnering to explore genetic and geographic ancestry to enhance medicines discovery and development.

Important lessons from these data for consumers, clinicians, and researchers (and for grouping by self-identification) include: (1) individuals often have multiple geographic ancestries, and (2) the genetic ancestries may be very different from what individuals believe and how they self-identify. Knowledge of genetic and geographic ancestry might also alert individuals to possible differences in responses to medications.

There is great promise for genetics and genomics to advance our understanding of disease and the discovery and development of new medicines and to improve health outcomes. However, an important concern is for data privacy and the potential for unintended consequences (i.e., discrimination) resulting from data disclosure. While safeguards exist in some countries such as the Health Insurance Portability and Accountability Act (HIPAA) and the Genetic Information Nondiscrimination Act in the U.S. and the General Data Protection Regulation (GDPR) in the EU, privacy cannot be guaranteed.[588] Further, the business model for some for-profit consumer genetic testing companies includes reselling customer genetic data to third parties for biomedical research, a right embedded within the terms of service or end-user license agreement that customers sign, but rarely read or understand. Better protections and better strategies, technologies and processes are needed to protect sensitive information while at the same time facilitating support for data sharing, scientific discovery and achieving cost efficiencies.[589]

[587] Cheng TL, Goodman E. Race, ethnicity, and socioeconomic status in research on child health. Pediatrics. 2015 Jan 1;135(1):e225-37.
[588] Sorani MD, Yue JK, Sharma S, Manley GT, Ferguson AR, Cooper SR, Dams-O'Connor K, Gordon WA, Lingsma HF, Maas AI, Menon DK. Genetic data sharing and privacy. Neuroinformatics. 2015 Jan 1;13(1):1-6.
[589] Hendricks-Sturrup RM, Lu CY. Direct-to-consumer genetic testing data privacy: key concerns and recommendations based on consumer perspectives. Journal of personalized medicine. 2019 Jun;9(2):25.

16.4 Recommendations

Key Takeaways and Recommendations for Sponsors, Investigators, Providers and Participants:

- The prevalence of genetic variants that impact disease can vary across populations.
- Increase diversity and inclusion of research participants in genomic and genetic research if the promises of genetic and genomic research are to benefit all. Greater representation of underserved and underrepresented individuals and from geographically-diverse populations will increase knowledge of genomic variants in population subgroups, increase understanding of the genetic and biological mechanisms linking social determinants of health to health and disease, and increase understanding of the extent to which ancestral origin serves as a marker of disease susceptibility.
- Encourage participants from diverse backgrounds to participate in genetic studies, to the extent possible, to increase the pool of information in genome-wide association studies.
- Gather post-approval data (e.g., through pharmacovigilance, electronic health records, and/or real world data) to inform research into differential disease burden and drug response.
- Increase awareness among participants from diverse ethnic backgrounds to understand and communicate the potential value of genomics research.
- Advance the use by the public of genetic ancestry testing to further precision medicine and its translation into practice for the benefit of all.

17. Stakeholder Roles, Responsibilities and Accountability in Promoting Diversity

Stakeholders—funders, sponsors, CROs, research institutions and sites, investigators and their study teams, patient and patient advocacy groups and others—all share responsibility for inclusion of diverse populations in clinical research and for health equity in general. All are accountable for their role in the effort and share, albeit with different responsibilities and functions, toward success. No single entity can achieve diversity alone; if it is not an affirmative commitment of all, insofar as their specific contribution to diversity may be important or impactful, it will fail. There are obvious interdependencies among the stakeholders as well, and for real change to occur, one entity must be comfortable holding another accountable if success depends upon it. That shared accountability may be concretized by contract (e.g., between sponsor and CRO, or between CRO and site) or informally by conversation and common alignment. While the sections in this chapter isolate the stakeholders individually as a means upon which to focus specific recommendations and for which each stakeholder may hold themselves accountable, we appreciate that success will take the commitment and efforts of all, and that accountability is shared.

In many aspects of clinical research, regulatory requirements are primary motivators for sponsor, institutional, and investigator behavior. With regard to diversity and inclusion, the regulatory framework in some countries including the U.S. creates expectations and offers guidance in promoting diversity (see Chapter 7 "Existing Regulations and Guidance") but does not mandate compliance. To a large extent, therefore, the responsibilities for increasing diversity and inclusion in clinical research rest, individually and jointly, with stakeholders. In this Guidance Document, we have considered factors that facilitate or limit progress in meeting diversity's goals. In this chapter, we first describe the cross-cutting responsibilities, opportunities, and roles for all stakeholders that are necessary if increased diversity is to be achieved. We then address each stakeholder (see Figure 48) and their roles and responsibilities in promoting diversity in clinical research. These suggestions are not exhaustive but are meant to stimulate creative development in translating ethereal goals into concrete action, a task that is always challenging.

Figure 48: Individual and cooperative stakeholder accountability

17.1 Cross-cutting responsibilities

How can a stakeholder determine if its approach to diversity and inclusion in clinical research is sufficiently clear, purposeful, and specific? How can leadership determine if its strategic intentions penetrate throughout the organization, that each member appreciates their role and contribution? Are operations aligned with the strategic goal and translated into specific and achievable outputs, each associated with metrics to help track progress?

Table 17 lists a set of overarching questions for any organization. We then discuss five cross-cutting responsibilities: setting the organization priority; statements of commitment; patient, participant, and public engagement; partnerships; and tracking progress.

Table 17: Organizational priorities to promote diversity in research

The following questions highlight the internal structure, messaging, and coordination across and throughout the organization to promote diversity in research
• Has the organization posted a public statement of commitment to diversity and inclusion in clinical research? • Does the organizational mission or corporate responsibility statement reference diversity and inclusion? • Does the strategic plan include programmatic goals related to diversity and inclusion? • Are those responsible for fulfilling expectation and/or driving implementation appropriately identified and positioned within the organization? • Are the operational requirements for achieving diversity coordinated across the necessary organizational components? • Does messaging and communication within the organization promote diversity and inclusion? • Are there organization-wide efforts to recruit and train a workforce that can effectively develop and implement a diversity agenda? • Has the organization allocated resources necessary to fulfill these functions? • Does the organization have metrics to measure expectations and plans?

17.1.1 Establishing diversity and inclusion as an organizational priority

We believe that increasing diversity and inclusion in clinical research is a matter of both scientific and social responsibility. For all stakeholders, commitment to diversity requires setting research priorities, developing scientific and clinical expertise, and allocating resources to address the needs of understudied and underrepresented populations. As discussed throughout this guidance, clinical studies are expected to consider the scientific goals of diversity when research priorities are established and then throughout the course of study development and implementation. Diversity is addressed in research design, definition of eligibility criteria, in the choice of settings and the performance of sites, in data analysis, and in research conducted once regulatory approval is secured. A commitment to diversity as a scientific priority may involve a decision to fund a research program that builds upon existing

evidence of variability, such as preliminary evidence of subgroup differences. In considering prioritizing science to address diversity, some research organizations may choose to fund or seek funds specifically targeting discovery efforts on conditions, subgroups, and regions that have been underserved by research. In all cases and given the well-described impediments to a more inclusive research enterprise, diversity requires intellectual and material investment by all stakeholders.

How diversity in study enrollment can support an organization's scientific mission, sense of social responsibility, and business goals will vary considerably depending on organization size and purpose. The effective promotion of diversity within an organization of any type, large or small, requires an understanding throughout the organization of diversity's purpose—what we have referred to as "The Case for Diversity in Clinical Research" (Chapter 2). Establishing diversity as a priority requires internal and external messaging to communicate how strategic planning, resource allocation, and staffing will bring out desired change. Biogen, for example, established diversity and inclusion as part of a long-term business strategy, the ultimate goal of which was to address health care disparity for underserved populations in their primary therapeutic areas (see "Diversity and Inclusion Strategies Model Checklist" and "Case Study: Embedding Diversity & Inclusion (D&I) within a Pharmaceutical Company" in *Toolkit*). The organizational approach was initiated as a leadership imperative but evolved through internal Diversity and Inclusion (D&I) strategies, translating into an environment where everyone had a voice, and external D&I strategies, focusing on business operations that supported a diverse culture. These efforts led to employee ownership of D&I and company-wide accountability, both preliminary steps towards broadening diversity and inclusion in clinical research.

Organizations should determine how each person in the organization can demonstrate and document their contribution to the goal of diversity and inclusion. Larger entities may create positions tasked with increasing diversity in clinical research and developing necessary expertise in implementation. Smaller organizations can create analogous duties for staff and also align or partner with outside organizations (e.g., hiring consultants for implicit bias training or to recruit patient representatives to comment on study design or written communications). To be of value, such functions must be positioned within and/or endorsed by the organizational leadership to have sufficient operational reach, influence, and authority.

In any organization, many different individuals, teams, and departments are involved in and have responsibilities for research planning, review, execution, monitoring, and oversight; increasing diversity therefore requires a business infrastructure to align efforts (and resources). For example, the adaptation of consent materials for specific populations based on input from participants, clinicians, and local ethics review must be coordinated with clinical operations, corporate legal, and compliance teams separately, and each must understand the importance of and be committed to inclusion. In-service training, therefore, will occur throughout the organization. Similarly, organizations should develop specific performance standards and metrics to track and recognize effective implementation. Establishing incentives to recognize achievement and innovation by individuals, component programs, and the organization as a whole, drives change and underscores the commitment to diversity. In a parallel example, Takeda undertook a global campaign to promote a "patient-centric culture" throughout research and development (R&D); every employee in R&D had a performance metric that helped to embed the patient-centric mindset shift across R&D, which was followed by the requirement that global program teams develop a patient engagement plan as a proactive roadmap for engaging patients and the broader patient community. The MRCT Center developed an exemplar logic model and key performance indicators (see "Introduction to Logic Models," "Logic Model: Accountability" and "Accountability KPIs" in *Toolkit*) that could similarly be adopted for motivating organization-wide change to increase diversity and inclusion in clinical research.

RECOMMENDATIONS

- Establish diversity, inclusion, and equity in clinical research as an organizational priority that is communicated by leadership as a core value of the organization.
- Commit to diversity by setting research priorities, providing cultural competency and training on implicit bias, diversity and inclusion for all employees and allocating resources to address the needs of understudied and underrepresented populations.
- Develop an organization-specific "case for diversity" to demonstrate how diversity in clinical research addresses the organization's scientific mission, social responsibility, and business agenda.
- Create positions (and, in smaller organizations, roles) primarily tasked with promoting diversity in clinical research, ensure adequate resource allocation, and build infrastructure to facilitate communication and coordination across component functions.
- Create organization-wide performance standards, metrics, and incentives that encourage, track, and reward effective implementation and progress toward diversity's goals.
- Capture specific metrics relating to diverse enrollment, including geographic diversity, underrepresented minority populations (e.g., race, ethnicity, sex, young and elderly, etc.) for other understudied populations.

17.1.2 Public statements of commitment to diversity in clinical research

Public statements of commitment to scientific and ethical standards and, specifically, to the inclusion of diverse participant populations in clinical research by the academic institutions and the pharmaceutical industry drive accountability, help set priorities for an organization, define mission and leadership focus, align operations with mission, establish performance expectations, enable decision-making, and justify resource allocation. We suggest all stakeholders involved in clinical trials, whether sponsor, funder, academic medical institution, hospital, care provider practice, community setting, or patient advocacy organization adopt a

statement of commitment to diversity and inclusion. We propose a simple statement (Figure 49), which can be modified as appropriate to the setting and situation:[590]

Figure 49: A model statement of commitment

Wherein an organization does not have robust programs to enhance diversity and inclusion in its contribution in research, the statement could be adapted to be aspirational (e.g., "…working towards inclusion") and modified later as approaches and tools are adopted. Transparent policy statements that call for inclusion in research based on demographic (e.g., race, ethnicity, sex, gender, age, national origin) and non-demographic (e.g., disease severity, comorbidities, concomitant medications, disability) factors will help to focus and drive action by all stakeholders involved in the science of clinical research.

RECOMMENDATIONS

- Adopt a publicly facing statement of commitment, supported with internal implementation and tracking plans, to the inclusion of diverse populations in clinical research.
- Review job descriptions, annual goals, and key performance measures to focus upon relevant roles and responsibilities for promoting diversity and inclusion in clinical research. These should be as specific as possible and reviewed annually.

[590] Ahmed HR, Strauss DH, Bierer BE. Committing to the Inclusion of Diverse Populations in Clinical Research. Therapeutic Innovation & Regulatory Science. 2020 Jan 2:1-3.

17.1.3 Incorporating the patient perspective

The meaningful involvement of patients and participants in the work of research sponsors and funders, CROs, academic facilities, clinical trial sites, and others is necessary if research is to be informed by and alert to patient perspectives and priorities. This is especially salient in research with individuals from diverse and underrepresented groups, for whom the goal of inclusion in research has not been met. Industry and academic stakeholders must therefore understand the participant's expectations of and experience in research within the social, financial, and cultural context in which it occurs.

Patient, participant, and community engagement in its many forms (see Part C "Broadening Engagement") also addresses a broader institutional responsibility. Incorporating the patient perspective permits an organization to establish research priorities and craft research questions that are specifically responsive to the health needs of underserved individuals and their communities.

Figure 50: Patient and community engagement as a corporate responsibility

Finally, by inviting patients into the organization and into the process of planning and implementation, patients and their communities become witness to the process of drug development, increasing accountability, and creating opportunities to effect change (Figure 50). How patients and their advocates may most effectively be involved in the drug development and clinical research process, and where and at what level(s) within the organization patient engagement will be most valuable, will depend on the specific work of the organization.

RECOMMENDATIONS

- Specifically address in the organizational strategic plan the engagement of diverse and representative patients, their advocates, and their communities so the organization is meaningfully informed by patient perspectives and priorities.
- Track and document the formal and informal mechanisms an organization adopts to engage patients at different organizational levels and throughout the clinical research lifecycle.
- Ensure that all stakeholders consider the perspectives of the various subpopulations to be treated with a new therapy during the product development process (see Part C "Broadening Engagement" and section 13.1 "Product development and lifecycle").

17.1.4 Promoting partnership and accountability along the research pathway

The performance of clinical studies involves a complex network of entities and individuals joined in formal and informal partnerships. The effective execution of plans to increase diversity requires individuals to acknowledge their roles and responsibilities in the process. Just as critical, it demands that each stakeholder holds their research partners accountable. For example, research sponsors and funders should require their various implementation partners, including CROs, research sites, and investigators, to achieve agreed-upon diversity targets in recruitment. At one level, this involves selecting a CRO and research sites that consistently perform according to plan and reviewing performance for future trials (see Part E, Section 13.4 "Feasibility assessments and site selection"). At another level, specific language in the sponsor contract with the CRO, and the CRO's clinical trial agreement with the research site, can outline expectations for the accrual of a diverse study sample. And at yet another level, sponsors and research sites need to understand their specific study populations by engaging and responding to representative advocates and participants. The joint development of diversity targets and strategies between partners creates a unified approach, a sense of involvement and responsibility, and facilitates budgetary and other resource coordination so that the costs, including those of potential mid-point course corrections, are anticipated.

In clinical research supported by government or private funders, grants and contract applications should be required to include study sample demographics and recruitment strategy documents, as should progress reports for non-competing and competing renewals. Acknowledging such stakeholder obligations sets expectations that will foster bi-directional conversation and collaboration to increase diversity. Figure 51 illustrates examples of how entities and individuals hold their research partners accountable in clinical trials.

Figure 51: Accountability in partnership

RECOMMENDATIONS

- Define specific expectations and obligations, cooperatively including all stakeholders and organizations involved in clinical research, with regard to increasing diversity and inclusion in research:
  - Contracts between sponsors and CROs, and between CROs and research sites, detail expectations (by number, percentage) for the recruitment and study of underrepresented populations, as it might do for overall accrual.
  - Costs associated with targeted strategies in the recruitment strategy document, and necessary course corrections, should be anticipated and negotiated by sponsors and CROs, and between CROs and research sites, and detailed in contracts and budget descriptions.

17.1.5 Tracking progress

Each stakeholder is responsible for driving improvement. To track progress each must assess its organization, program, site, or study against relevant diversity goals and endpoints. Strategy and execution of diversity initiatives at the level of the research sponsor, the contract research partner, and the research site will differ, as the role each stakeholder plays in planning and implementation differs. Research sponsors and funders should address diversity and inclusion in regard to their research agenda — to what extent does the sponsor's overall research program, clinical trial portfolio, workforce, and recruited populations support the vision of diversity in research? CROs and sites must plan for effective implementation, set diversity goals, anticipate impediments or challenges "on the ground," and establish review benchmarks to trigger course corrections when those goals are not met.

Each stakeholder must identify specific measures of progress and then track whether their research program, study, site, or individual investigator meets these expectations. Just as data on participant accrual and retention are used as a performance indicator, fulfillment of demographic goals should be routinely monitored. Examples of specific measures of performance related to diversity goals may include:

- A large drug and device manufacturer develops a 5-year plan to increase the participation of racial and ethnic minority patients in all of its oncology programs. It gathers data annually on trial participation for its entire phase 2, 3, and 4 portfolios.

- A CRO collects demographic data on participant enrollment. Periodically it compares enrollment to the recruitment strategy document, and introduces helpful corrective actions when enrollment deviates from plan by a certain percentage.
- A clinical site tracks demographic data on potential participants referred by clinicians.
- An institution annually compares the demographics of the patient population to the demographics of participants enrolled in research, arrayed by therapeutic area, program, clinic, or investigator.

As described in Chapter 11 "Data Variables and Collection," standardization of the method of ascertainment and categorization of individuals according to demographic groups is an essential starting point. Yet progress in the field will ultimately derive from additional changes in clinical research; success will require development of performance metrics to chart progress and hold oneself and one another accountable (see "Accountability KPIs" in *Toolkit*).

RECOMMENDATIONS

Each stakeholder:

- Adopt uniform demographic variables to promote consistent data acquisition, analysis and reporting.
- Require, as relevant, a description of the demographic and non-demographic variables of the research population in funding proposals, research plans, progress reports, continuing reviews, final reports, and publications employing uniform data variables and reporting formats.
- Develop common data standards for those variables that are not currently standardized (e.g., social determinants of health) including scripted recommendations on methods for data collection.
- As these standards are developed, include the requirement to report these additional variables publicly such as in clinical research registries (ClinicalTrials.gov, EudraCT, WHO ICTRP).
- Use accrual of participants within pre-specified demographic categories, like overall participant accrual, as a key performance indicator and chart progress within organizations and in response to initiatives.
- Adopt metrics to track performance in relation to their diversity goals and plans and specific diversity initiatives.

17.2 Industry sponsors and other entities that provide funding for clinical research

For industry sponsors, embracing diversity involves a commitment to scientific priorities that are relevant to the needs of diverse populations. Corporate leadership should direct intellectual and material resources to the study of therapies for understudied conditions, subpopulations, and communities. Clinical trials can be designed to directly examine or be sensitive to existing evidence of variability, and to optimize the detection of subgroup differences through robust

and innovative data analytic strategies. As discussed above, sponsors must select research partners, community partners, and clinical research sites that are similarly committed and capable of promoting diversity and inclusion. Sponsors can also engage with a diverse group of patients or participants to understand their perspectives and encourage bi-directional discussions on study design and inclusivity. As a practical and measurable endpoint, sponsors should ensure that clinical trial participation reflects the demographics of the conditions of interest.

Other entities, including government and foundations that provide funding for clinical research, are similarly capable of promoting diversity. They may set expectations or requirements for the recruitment of diverse and representative samples or require the inclusion of specific subgroups. They may solicit proposals for projects that examine conditions and diseases prevalent in understudied populations or may support research that tests methods to enhance and track diversity in recruitment or to increase retention. Similarly, funders may consider research that explores innovative approaches to statistical evaluation of heterogeneity. Funders could support research that studies issues pertinent to health disparities and health equity such as the interplay of treatment efficacy and the social determinants of health is vital to health disparities research. Importantly, funders should always require grantees to report recruitment and retention of subgroup populations compared to the funded proposal. By holding grantees accountable, and by prioritizing funding for investigators and institutions with a track-record of success in recruitment, retention, and analysis of diverse populations, funders can meaningfully contribute to the goals of increasing inclusion in clinical research.

Industry sponsors and other entities that engage in and fund research have a pivotal role in helping CROs, sites and investigators increase representation of diverse populations. As a precompetitive contribution, sponsors can share and publish methods related to effective patient engagement, successful recruitment and retention strategies, and data analysis. Sponsors and other funders should respond to public requests for information by health authorities, providing comments on draft regulatory guidance and regulation to foster bidirectional communications and inform public discourse.

RECOMMENDATIONS

- Include research on and with populations who are underrepresented and understudied among a sponsor's or funder's scientific priorities. These priorities can be included within the sponsor/funder's mission statement, enumerated in product development plans or requests for proposals, tracked and publicized in the organization's research portfolio and in the demographics of studies funded and completed.
- Create partnerships between and among patients, participants, and the public to be responsive to the needs of affected populations, their priorities, and perspectives. Engage patients, participants, and the public early in product development and commit to long-term relationships to increase trust and understanding of affected populations and community needs. Additional recommendations related to participant and community engagement can be found in Chapter 8 "Participant and Community Engagement."
- Establish community relationships to promote awareness and knowledge of clinical research. Additional recommendations related to increasing participant awareness and knowledge can be found in Chapter 9 "Participant Awareness, Knowledge and Access."
- Request for applications for grants and contracts should require the applicant to (a) evaluate whether and how the research will contribute to the goals of diversity, if applicable, and if not, why not; and, in any proposal involving clinical research, (b) include a feasibility and tracking plan for the enrollment of diverse and inclusive populations, (c) describe the recruitment and retention plan specific for underserved populations, (d) adopt common data and metadata standards for data collection, (e) report demographic information in periodic reports and competitive renewals, (f) provide evidence of prior work demonstrating successful accrual and retention of diverse populations, (g) commit to returning results to participants, and (h) share data and publication of results relevant to the analysis of variability within clinical populations.
- Make continued funding dependent upon meeting specific enrollment objectives and aims relevant to the goals of diversity. This should be assessed mid-course, and, if

accrual is not consistent with the proposal, a written justification for the departure and a corrective action plan should be submitted and reviewed. As appropriate, the funder may choose to review the results from implementation of the corrective action plan at more frequent intervals.

- Ensure there is diversity in the workforce and train employees in the skills necessary to support, understand, and communicate with a culturally diverse team. Additional recommendations can be found in Chapter 10 "Workforce and Diversity: Training and Development."
- Create organizational goals related to diversity and inclusion, both internally within the organization's workforce and externally among vendors, contractors, and clinical research sites.

17.3 Contract research organizations

A contract research organization (CRO) is responsible for implementing and executing the sponsor's goals for recruitment of the intended population, including planned inclusion of diverse populations. CROs should anticipate the request for a detailed plan of recruitment methods from its sponsor/customers, be prepared to respond to questions regarding the CRO's capabilities to implement the plan, develop expertise in recruitment and retention of diverse populations, be able to track performance, and adhere to the expectations specified in contractual agreements. Advanced planning, staff training, and the development of a network of sites with demonstrated capability in the recruitment of diverse populations will help stimulate the accrual rate including of diverse participant populations.

A CRO should develop, collect, and validate performance metrics to demonstrate its ability to implement clinical trials in diverse populations. In any particular clinical trial, a mix of clinical research sites may be necessary to achieve the proposed overall study population demographics (see Section 13.4 "Feasibility assessments and site selection"). Similarly, a formal feasibility assessment of sites should be performed by CROs, and CROs should formally request appropriate evidence of enrollment of diverse populations from any site under consideration for selection. Simply asking for these data will increase investigator and site attention to

diverse and inclusive enrollment. CROs may then select and contract with clinical research sites that provide evidence of appropriate workforce characteristics and training, required language skills, cultural competency, and either a history of demonstrated success or a thoughtful, comprehensive plan for recruitment. CRO budgetary considerations for investigator/site budgets must account for costs of efforts necessary to identify, recruit, and study a diverse population (e.g., extended clinic hours, translation of documents (see Section 13.5.2 "Study conduct and retention"). CROs should solicit input from clinical trial participants, advocacy groups, and site investigators to inform strategy and to guide site selection. Sample questions that can be used by a research sponsor in its Request for Information during the process of selection of the CRO as a preferred partner are listed in Figure 52. CROs should maintain a database of site performance to refer to for future site selection.

Figure 52: Sample questions used by a research sponsor to assess selection of a CRO

In its process to identify and select preferred CRO partners, the following are examples that a clinical trial sponsor could consider in its Request for Information from applicant CROs.
• Does your organization have a statement on commitment to diversity? If so, how is it backed by an implementation strategy? • What is understanding of diversity and inclusion in clinical research? • Is your workforce trained in cultural competence? In implicit bias? • What is the diversity of your workforce? Of the individuals you plan to assign to this engagement? • Provide the demographics of participants in the last 5-10 trials you have managed. • Provide the three most successful trials in which diverse populations were enrolled: I. What were the elements of success? II. What were the challenges? III. How did you address those challenges? • What is your plan to achieve the specified population for this trial? • How do you include expectations of diverse enrollment in your feasibility plan? • What is your process for site selection with regard to diverse enrollment? • How do you track demographics of site enrollment over time?

- With what periodicity do you review overall enrollment by demographic?
- What is your approach to recruitment using social media?
- Do you work with or engage with patient advocacy groups?
- Do you have a standing patient advisory group(s)? In which therapeutic areas?
- Do you partner with companies that have expertise in diversity & inclusion?

We encourage the publication by CROs and others of successful—and failed—methodologies for recruitment and retention. As sponsors and funders concretize their commitment to inclusion of diverse populations, the ability of CROs to meet those expectations in a time-sensitive and resource-efficient way will become a competitive advantage and a differentiator.

RECOMMENDATIONS

- Develop necessary expertise, organizational goals, operational capacity, and relationships with both sponsors and clinical research sites in order to recruit and retain diverse and inclusive study populations:
  I. Anticipate the request for a detailed plan of recruitment methods and be prepared to respond to questions regarding implementation capabilities.
  II. Develop and document methods for recruitment and retention of diverse populations, including how to track performance and adhere to expectations specified in the contractual agreement.
- Develop an inventory of successful operational tools, including best practices for aligning data collection and reporting standards.
- Include specific questions in the feasibility assessment of investigators and research sites related to recruitment and retention of diverse populations, develop a database of responses annotated by results.
- Ensure research contract specifies performance expectations with regard to enrollment and retention of an overall diverse study population.
- Develop, collect, and monitor the ongoing performance of investigators and research sites in fulfilling commitments regarding diversity and develop corrective interventions in real time if a site or investigator fails to meet contractual obligations.
- Select and contract with clinical research sites that demonstrate appropriate workforce training, required language skills, cultural competency, and a commitment to diverse inclusion in research.
- Develop performance metrics to measure the CRO's ability to meet the expectations of the sponsors.
- Ensure there is diversity in the CRO workforce and train employees in the skills necessary to support, understand, and communicate with culturally diverse clinical research teams. Additional recommendations can be found in Chapter 10 "Workforce and Diversity: Training and Development."

17.4 Academic research institutions and healthcare facilities

Although individual commitments vary, academic and healthcare facilities invest in the development of infrastructure that facilitates the treatment of, care for, and inclusion of diverse, underserved, or hard-to-reach populations. In clinical research, academic and healthcare facilities build, or can build, capacity, workforce, expertise, research infrastructure, and oversight for clinical investigators relevant not only to clinical research but to inclusion of diverse populations in a clinical trial.[591] Institutions invest, or can invest, in the creation of highly visible institutional centers, committees, positions, and roles to promote diversity and inclusion in research. Effective workforce development and training to promote diversity requires strategic planning and appropriate allocations of resources (see Chapter 10 "Workforce and Diversity: Training and Development") and will be impactful—beyond research activities—in clinical and supportive care. Institutions that have created robust linkages with community and advocacy organizations and that have recruited and trained a workforce that is itself diverse, as well as those that consistently meet recruitment goals, will have a competitive advantage for selection by funders, sponsors, and CROs. Academic and healthcare facilities can track metrics for results, developing data-driven strategies and a successful framework; grants offices and ethics review committees can oversee performance; and internal funds can be used to support centers of excellence and to create appropriate incentives to study underrepresented populations. For example, an institution's grants and contracts office can educate research staff on regulatory expectations with regard to diversity, provide templates and guidance to simplify efforts to develop appropriately responsive funding applications, and direct organizational funds to support staffing, expertise, and infrastructure. Institutions can educate and train non-research clinicians about clinical research, cultural competency, diversity and inclusion; about specific trials available; and about implicit barriers to diverse participation in clinical research and its implications on scientific impact. Finally, facilities will need to secure interpreter services if a proportion of potential participants do not speak the native language, as well as health-literate educational materials and trial navigators, if possible.

[591] Certain available resources may be helpful. See the Society for Clinical Research Sites, "Diversity in Clinical Trials." Available at https://myscrs.org/learning-campus/diversity-in-clinical-trials/. [Accessed 2 July 2020].

Significantly, it is important for academic research institutions and healthcare facilities prioritize training and support of a diverse work force, with attention to minority and under-represented investigators, and providing mentorship for junior investigators to help ensure success. Programs to permit both junior and community 'associate' investigators to participate—and be visible—in clinical trials, mentored until comfortable becoming primary investigators, for instance, would be one approach.

RECOMMENDATIONS

- Adopt a statement of commitment to diversity and inclusion to help set priorities for the organization and drive accountability.
- Develop and drive organizational-wide efforts to recruit and train a diverse workforce.
- Establish positions, roles, or centers tasked with promoting diversity in clinical research.
- Invest in the development of infrastructure that facilitates the treatment, understanding, and inclusion of diverse, underserved, or hard-to-reach populations.
- Draw upon and align existing capacities and infrastructure in community outreach and engagement, research recruitment, research oversight, and workforce training to facilitate diversity and inclusion in research.
- Identify specific motivational constraints that serve as impediments to referral by non-research clinicians and work with clinicians to develop solutions.
- Ensure interpreter services are available for clinical research sites.
- Promote the development of health literate and translated resources that explain clinical research generally so that patients understand the nature of research in advance of being asked to participate.
- Provide "participant navigators" for select participants who may need support for study completion.

17.5 Clinical research sites

Clinical research sites (also referred to as "sites") operationalize and execute engagement, recruitment, and retention strategies. The development of a trial-specific recruitment strategic document requires the adaptation of trial logistics to align with the values and practical needs of local communities. Building capacity for diversity, inclusion, and equity at the site entails re-evaluation of site staffing and staff training (see Chapter 10 "Workforce and Diversity: Training and Development").[592] Importantly, sites must learn to be attuned to implicit bias in the identification and selection of eligible research participants. Similarly, the approach to recruitment, through advertisements and community education, must be responsive to information gathered about subgroup motivation to participate in research, barriers to access, and patterns of referral of diverse populations (see Chapter 8 "Participant and Community Engagement" and Section 13.5.1 "Recruitment and recruitment strategy document"). These steps necessarily follow systematic outreach by clinical research sites to engage and learn from prospective participants.

A clinical research site may, or may not, be associated with an academic research institute or healthcare facility (see Section 17.4 "Academic research institutions and healthcare facilities"). For those associated with an academic research institute or healthcare facility, there are benefits from the larger organization's research infrastructure to promote diversity. For example, clinical research sites can rely upon the parent organization's community engagement activities, interpreter services, patient and family advisory boards. Conversely, a clinical research site may develop specific skills, knowledge, and relationships as a result of its location. For example, a site located in a neighborhood with a predominantly African American, South-Asian immigrant, or Spanish-speaking population may develop expertise with specific disease conditions, language, and community engagement practices that is important both for advancing diversity in clinical research and to extend the capacities of the parent organization.

Designing and building clinical trials infrastructure necessary for research with understudied groups requires an investment in effort, time, and human resources. The investment will be worthwhile as funders, sponsors, CROs, and other organizations select clinical research sites in part based on their ability to recruit the populations to which they commit.

[592] Certain available resources may be helpful. See the Society for Clinical Research Sites, "Diversity in Clinical Trials." Available at https://myscrs.org/learning-campus/diversity-in-clinical-trials/. [Accessed 2 July 2020].

RECOMMENDATIONS

- Ensure there is diversity in the clinical research site workforce.
- Encourage career development and leadership opportunities for people with diverse backgrounds.
- Train employees in the skills necessary to support, understand, and communicate with a culturally diverse team, especially those who have direct communication with patients and participants. Additional recommendations can be found in Chapter 10 "Workforce and Diversity: Training and Development."
- Require investigator and study team training in good clinical practice and in the ethics of human participant research – ensure modules emphasizing the scientific and ethical value of diversity and inclusion in research are included.
- Establish community partnerships, potentially with a focus on the disease condition of study, to understand the needs and burdens of their potential participants, including those in underserved and underrepresented communities.
- Educate sites in known operational and work-force related barriers to the inclusion of diverse population.
- Ensure the physical space of the clinical research site is culturally welcoming and acceptable to all participants and adheres to physical handicap requirements.

17.6 Principal investigators and study teams

Principal investigators (PIs) and their study teams play a critical role in the execution and conduct of a study and have a responsibility to research participants and the scientific community to be as inclusive as possible. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice E6(R2) (ICH GCP E6(R2)),[593] an international guideline that outlines ethical and scientific quality standards for the design, conduct, performance, monitoring, auditing, recording, analyzing, and reporting of clinical trials, states that the PI is responsible for ensuring all study procedures are followed

[593] ICH GCP is available online at: https://ichgcp.net/

and that all study staff are compliant with the ethical principles in the Declaration of Helsinki.[594] With regard to diversity and inclusion in research, PIs and their study staff are the gatekeepers as to whom is invited into the research; they should be aware of the value of diversity in research. As the main contact point for participants, the team should strive to foster understanding of and rapport with participants, be sensitive to the different barriers that minority and underrepresented populations face (see Chapter 8 "Participant and Community Engagement"), and be creative in response to necessary accommodations. Workforce development, GCP training, and implicit bias training undergird successful recruitment and retention of diverse populations (see Chapter 10 "Workforce and Diversity: Training and Development"); PIs and their study teams should seek feedback from patients, caregivers and the healthcare professionals with whom they engage.

[594] World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization. 2001;79(4):373. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ [Accessed 22 June 2020].

RECOMMENDATIONS

- Endeavor to reflect a diverse clinical research team.
- Encourage professional development and networking opportunities for individuals of diverse backgrounds.
- Train clinical research team in the skills necessary to support, understand, and communicate with culturally diverse participants, especially those team members who have direct roles in recruitment, informed consent, and study visits.
- Ensure investigators and study teams are capable of engaging in thoughtful conversations related to the purpose and the potential burdens of the research study and procedures and equipped to address potential flexibilities in study conduct (additional recommendations can be found in Chapter 10 "Workforce and Diversity: Training and Development").
- Train PIs and study teams in ICH GCP and implicit bias.
- Solicit feedback from patients, caregivers, and other healthcare professionals on the study team and PI's conduct and behaviors throughout the study timeline.
- Establish relationships with non-research clinicians and referring physicians to ensure familiarity of research in general, as well as providing information on specific studies that may be beneficial to their patient population.
- Ensure study aims, procedures and eligibility criteria are provided in a user-friendly format and remain engaged with referring physician during participant's time in clinical study. At end of study, provide referring physician with information related to nature and outcome of study and return the patient for further care.
- Establish community relationships to promote awareness and knowledge of clinical research. Additional recommendations related to increasing participant awareness and knowledge can be found in Chapter 9 "Participant Awareness, Knowledge and Access."
- Track past performance with regard to enrollment and retention of diverse populations in order to provide historical and potential feasibility to sponsors and CROs seeking clinical research sites.

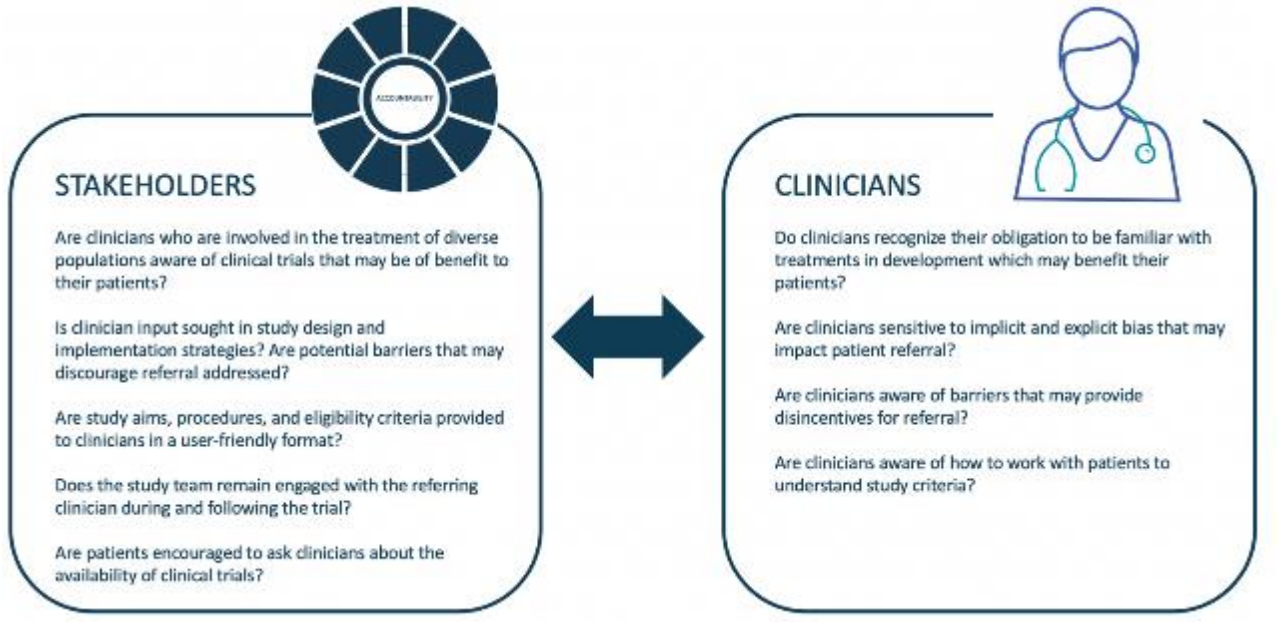
- If non-English speaking participants are expected to be recruited and enrolled in the research study, ensure study team speaks the native language of participants or interpreter services are available.
- During the research study, engage with participants to ensure that they are not unequally burdened by procedures or travel to clinical research site. Inquire as to whether participants have additional questions or whether further assistance is needed.
- Return aggregate and, to the extent possible, individual study results to study participants.
- Return aggregate results to the community if relevant, in a language and manner that will be received and adopted by the community.
- If appropriate, secure continued access to the investigational product for the participant population if participants are benefitting and have no other equivalent options for treatment.

17.7 Referring clinicians and health care professionals

Non-researcher clinicians and other medical professionals play a role in identifying and referring patients for consideration for potential clinical trial participation. To do so, clinicians must be made aware of locally available clinical trials that may serve the interests of their patients and for which their patients may be eligible. In certain medical specialties, where clinical research may provide novel therapies for treatment of refractory patients, clinicians have an affirmative obligation to familiarize themselves with available treatments in development. Finally, other stakeholders should recognize and respond to the fact that non-research clinicians may need to be introduced to a trial finder (e.g., ClinicalTrials.gov, EudraCT, WHO ICTRP) or may require incentives and assistance to overcome barriers to involvement, such as the significant time constraints associated with medical practice.

Clinicians and clinical investigators who provide care to patients have a fiduciary responsibility to serve the best interests of their patients. In this capacity, patients generally trust their healthcare providers. When properly informed by the research team, clinicians may consult and advise individual patients about the potential benefits, risks, and scientific importance of participation. Clinicians can also provide valuable input regarding clinical priorities, patient priorities, and aspects of clinical trials that encourage or impede participation (see Figure 53).

Figure 53: Interaction between stakeholders' and clinicians' responsibilities and engagements



RECOMMENDATIONS

- Periodically communicate with clinicians about research opportunities and trial availability. Such information must be educational—not promotional—in nature and made easily accessible, digestible, and include information that can be shared with patients.
- Seek to be familiar with research and the potential research opportunities that may benefit their patients.
- Ensure referral of patients is not impacted by implicit or explicit bias.
- Commit to helping patients understand the difference between research and clinical care.
- Provide feedback to research site leadership, CROs, and sponsors to improve research benefit and lessen the burden to participation. Non-research clinician advisory panels can be convened to identify clinical (patient) priorities.

17.8 Patients and patient advocacy groups

Patients and research participants, individually and through groups that advocate for them, are uniquely positioned to influence the direction and priorities in research. Through the lens of diversity, it is important that patients, participants, and advocacy groups represent the populations of interest: different individuals and different groups, whether differentiated by disease or condition, age, ethnicity, or other parameter, have different perspectives that need to be considered. Advocacy group interactions are helpful as a source of information and of patient referral.[595] The voice of the individual, and of the individual who is new to research, however, differs from the perspectives of professional or established organizations that are dedicated to, and knowledgeable about, research. While all these perspectives are important, relationships with individual representatives of diverse subgroups should be sought.

[595] Advocates and patient organizations do not necessarily represent the "ordinary" non-activated patient and should not be the only means of getting patients perspective in research.

Patients[596] who may participate, and individuals who have participated in clinical research, and often their families or guardians, provide feedback to study teams, facilities and sponsors. These individuals may also valuably serve on research oversight committees, community advisory groups, and patient and family advisory committees. Whoever is engaging these groups or soliciting input should make sure that the final group selected represents the intended population for the trial or for the product. Either individually or by engaging with advocacy and community organizations, patients can inform investigators and other stakeholders about their lived experience, questions of personal importance, improvements to the planned conduct of research, and can thereby impact investigator competencies in a manner that better serves shared goals.

Advocacy and community groups are informed partners and help not only with study questions and design but also with development and execution of recruitment, enrollment, and retention plans. Advocacy groups organize and communicate on behalf of patients and participants, provide resources to facilitate and encourage patient involvement, and train other stakeholders. In addition, advocacy organizations can promote education about clinical research, advise on the availability of specific research opportunities, and answer questions about research participation. In addition, a number of advocacy organizations have organized searchable databases of available trials, useful not only to patients but also to clinicians and healthcare providers. Finally, advocacy organizations, through legislative outreach, can effectively support research, specify research priorities, and underscore the importance of inclusion.

[596] In this context, the term "patients" is used to refer to individuals affected with the disease or condition of interest or healthy volunteers depending upon the research question.

RECOMMENDATIONS

- Disease-focused patient and research advocacy organizations: undertake diversity initiatives to engage, inform, and empower understudied groups regarding clinical research.
- Patient advocacy groups: Through outreach and engagement of understudied groups, develop expertise in effective approaches to recruitment and retention of diverse populations; disseminate this information through publication, consultation, and researcher education.
- Patients representative of the demographics of a disease: engage in advocacy and community organizations, where they can influence relevant components of the conduct of clinical research.

17.9 Regulatory agencies

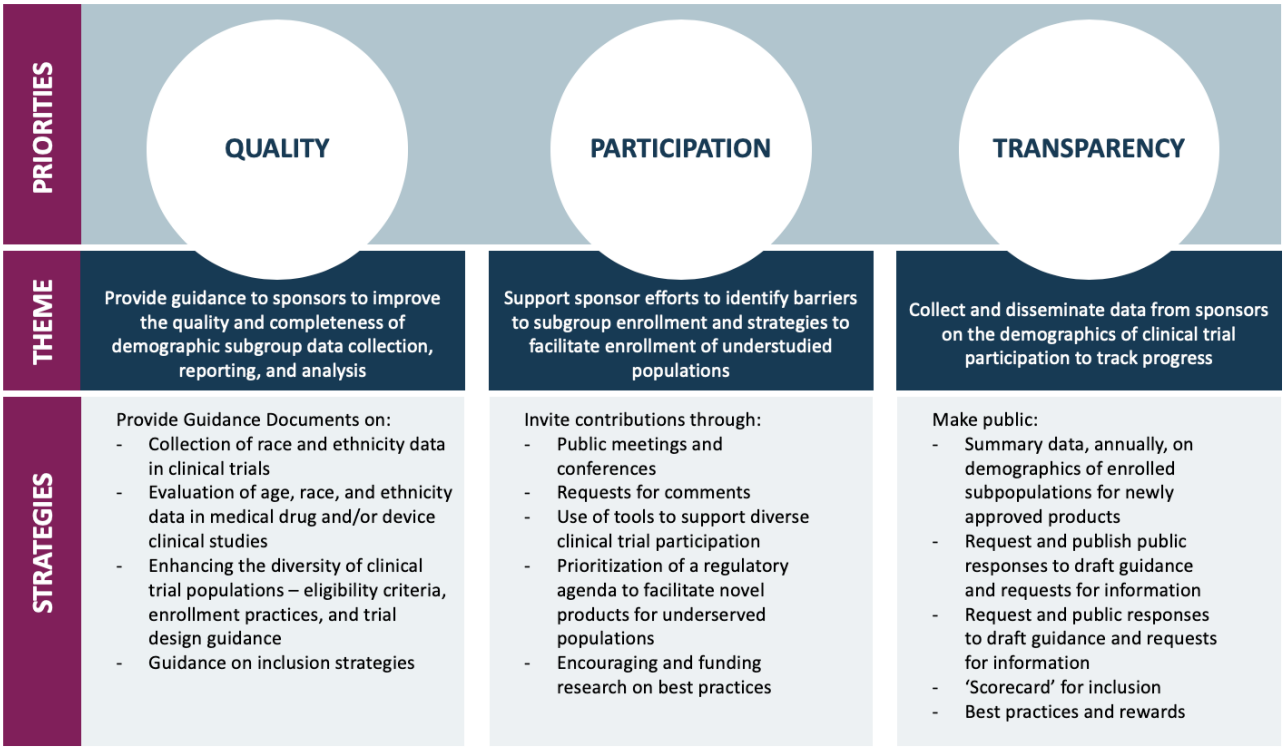
In the otherwise highly regulated world of clinical trials, efforts to promote diversity and inclusion occur in the absence of a comprehensive regulatory mandate and with few areas of specific requirement. Incentives for action, such as the extension of market exclusivity to promote pediatric drug research offered in the U.S. FDA Modernization Act of 1997,[597] do not exist within the regulatory framework to address diversity and inclusion.

At the same time, most regulatory authorities have worked effectively within their statutory authority to improve the quality and completeness of capture and reporting of clinical trial demographic data, help the field identify barriers to inclusion to facilitate enrollment of diverse populations, and publish data on the demographics of trial participation for approved drugs to promote transparency (see Figure 54). Such activities by the U.S. FDA have served to focus attention on the current state of diversity in research, provoke conversation within the medical literature and in the lay press, and stimulate the field more broadly to identify and address

[597] 105th U.S. Congress (April 23, 1997). "H.R.1411: Food and Drug Administration Regulatory Modernization Act of 1997". *U.S. House of Representative Bill Summary & Status*. Library of Congress THOMAS. Retrieved March 23, 2013.

impediments to more diverse clinical trial participation. Further, this focus on enhancing participation, the quality of data acquisition, and transparency in the tracking of progress in diverse enrollment (see previous discussion of "FDA Drug Trials Snapshots" in Section 5.2), provides a prototype for action by other regulatory entities and others involved in the oversight of industry clinical research.

Figure 54: Suggestions for regulatory action plan priorities to promote diversity and inclusion in clinical research

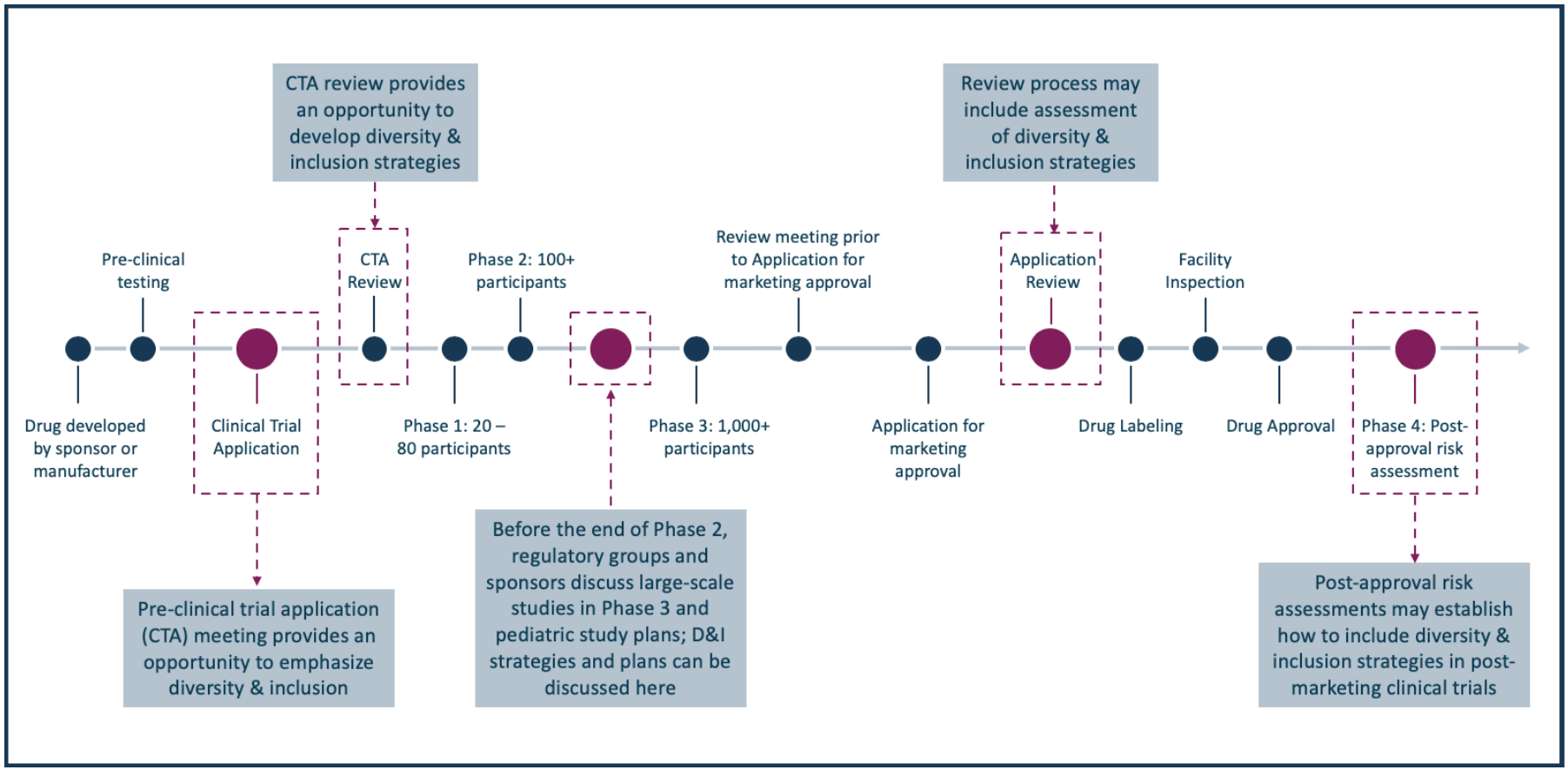


As described in Figure 54, regulators[598] can encourage and facilitate progress in the development of standards for the collection and reporting of demographic data and in developing novel approaches to data tracking and analysis. Active outreach by regulators to research sponsors and other stakeholders through public solicitation of information and

[598] National health regulatory authorities are generally limited in their ability to mandate certain activities based on the laws and regulations of their country. If mandates are permissible by law, they must be well conceived, specific, and actionable to produce the desired impact. Despite the intention, mandates may also fail to generate the intended change in behavior.

requests for comment on draft guidance and on regulation reflect important avenues for advancement and coordination of effort. Regulators provide direction and guidance to sponsors regarding when to address diversity and inclusion during the drug approval process (Figure 55). Wherein biological efficacy or safety is known to correlate with a demographic or non-demographic variable, regulators can review the applicant organization's product development plans for study of those subgroups, review the clinical trial recruitment strategy document specifically for attention to the inclusion of those subgroups, ensure that the recruited population reflects the plan, and clearly identify that the label for the product is specific to the population studied. Finally, regulators may convene meetings of stakeholders to stimulate conversation on the refinement of data collection and analysis; they may develop and refine tracking tools (e.g., FDA Drug Snapshots) that bring transparency to the research performed.

Figure 55: Opportunities to address diversity and inclusion during the drug approval process



RECOMMENDATIONS

- Support sponsor efforts to identify barriers to subgroup enrollment and strategies to facilitate enrollment of understudied populations through educational initiatives, conferences, and publications.
- Provide direction to sponsors to improve the quality and completeness of demographic subgroup data.
- Collect and disseminate data from sponsors on the demographics of clinical trial participation to track progress.
- Actively engage sponsors and investigators to solicit feedback on draft guidance and regulation relevant to diversity initiatives.

17.10 Institutional Review Board (IRB)/Research Ethics Committee (REC)

All clinical trials require institutional review board (IRB) (or alternatively, research ethics committee [REC]) review and approval, and most are subject to ongoing or continuing IRB/REC review and approval, typically occurring at least annually. IRBs and RECs are tasked with evaluating research proposals against prevailing regulatory standards and ethical requirements (in the U.S., FDA[599] and HHS[600] requirements and the principles of the Belmont Report,[601] respectively). We believe that the oversight of research with attention to the inclusion of understudied populations falls well within the regulatory and ethical purview of IRB/REC review and offers a valuable approach to oversight and accountability that can further the aims of diversity. We have previously discussed the role of the IRB/REC review in promoting diversity in Chapter 14 "The Role and

[599] CFR - Code of Federal Regulations Title 21, accessed at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50 [Accessed 22 June 2020].
[600] https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html [Accessed 22 June 2020].
[601] U.S. Department of Health and Human Services. Office of the Secretary. The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Available at: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html#xjust. [Accessed 22 June 2020].

Responsibility of the IRB/REC in Inclusion and Equity." Detailed recommendations to ensure oversight and promote diversity are provided in that section.

IRBs are well situated to identify opportunities to broaden overly narrow or restrictive eligibility criteria and identify and minimize risks associated with their inclusion. Re-orienting oversight from a focus on "protection" to one that considers the balance of risks and benefit of inclusion requires education for IRBs and new tools to guide review.

RECOMMENDATIONS
• Ensure the IRB/REC is composed of a diverse group of individuals and ideally represents the local underserved and minority communities. • Train IRB members to be culturally aware and sensitive to local underrepresented and underserved groups. Additional recommendations can be found in Chapter 10 "Workforce and Diversity: Training and Development." • Revise policies, standard operating procedures, investigator and IRB staff human participant education requirements, and tools and checklists so that they incorporate review and oversight of diversity and inclusion in research at initial and continuing review. Detailed recommendations can be found at the end of Chapter 14 "The Role and Responsibility of the IRB/REC in Inclusion and Equity."

17.11 Journal editors

Transparency related to efforts to increase diversity promotes accountability and is itself a tool to stimulate collaboration, change, and dialogue. The sharing of innovative and successful (or failed) strategies promotes best practices in efforts to address the impediments to diversity and allows for the iterative development of common metrics to track progress towards the goals of diversity.

In other domains, biomedical journal editors and publishers have established standards and effectively promoted disclosure and transparency related to investigator financial conflict of

interest,[602] clinical trials registration,[603] and data sharing.[604] Similar to the expectation for submission of diversity plans at the time of IRB review described above, journal editors need to consider new approaches to encourage the sharing of information relevant to diversity initiatives. In addition, journal editors and publishing houses should be as objective as possible during their selection and review process. The importance of maintaining neutrality cannot be sufficiently underscored; implicit bias training may be warranted for journal editors and reviewers. We believe impartial, routine, detailed, and widespread publication of study population characteristics creates accountability and would help to motivate needed change. Requirements for standard analysis of data by sex and/or age and other defined parameters would similarly foster progress and should be encouraged; pre-specified analyses should be differentiated from post-hoc statistical analyses.

RECOMMENDATIONS

- Establish policies requiring as a condition for publication of manuscripts, the submission for review of demographic characteristics on the enrolled clinical trial sample, including sex, age, race, and ethnicity, study inclusion and exclusion criteria, and method of ascertainment.
- Require comment from author regarding the generalizability of the research findings as they relate to underserved or underrepresented groups.
- Be objective, impartial, and inclusive when selecting and editing publications.

[602] http://www.icmje.org/recommendations/browse/roles-and-responsibilities/author-responsibilities--conflicts-of-interest.html [Accessed 22 June 2020].
[603] http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html [Accessed 22 June 2020].
[604] http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html [Accessed 22 June 2020].

18. Future Considerations and Conclusions

We have outlined both theoretical and practical considerations for increasing diversity, inclusion, and equity in clinical research. We have based the foregoing on the literature, personal experience, contributed examples, and advice. We know, however, that this work is just beginning and is far from complete—there is much we do not know and much to learn.

Empirical data to learn what works well, under what conditions, for which populations, and for which individuals are lacking. A commitment to a research agenda to discover successful approaches that are workable—and to understand when and how they should be deployed—should be prioritized. In addition to practical approaches to increase diversity (e.g., community engagement, alternative recruitment methods, participant accommodations, workforce training and development), there are fundamental gaps in knowledge that should be addressed. Genetic databases, for instance, are skewed towards the Global North and towards individuals of Anglo-American and European descent. Forward progress in personalized medicine, and the ability to advance treatment for all individuals, will require adequate representation and genetic diversity. Similarly, an understanding of pharmacogenetics and pharmacogenomics demands broad representation, and that diversity is useful scientifically for deductive interpretations of significance. In the absence of broad representation, it is far more difficult to assign functional importance to allelic variation.

In addition to a research agenda, work to develop, harmonize, and adopt common definitions and terms of use is needed. There is no global standard—or often national standards—for categorizing social determinants of health, nor is there an understanding of how to ask questions that will illuminate important differences in social determinants of health. Similarly, there is no accepted delineation of which dimensions of social determinants are most important or whether any can serve as surrogates for others. How is salary or income related to wealth and which is more important? Is the number of children living in a household more or less important than the number of individuals living together? Does food insecurity track with earned income? How is educational attainment related to other factors? Finally, how does an investigator or study staff ask these questions respectfully, particularly as many of these factors appear to be sensitive and quite personal?

Although the common lexicon often substitutes gender for sex, these terms are distinct. And while not all research questions require identification of gender, there is no accepted standard

for categorizing gender identity. Demographic questionnaires that assume gender binary distinctions can be offensive and alienating to individuals who think of themselves differently. Different people think of terms differently, and different societies have different understandings of gender differences. Because we lack a common language, and in its absence, just like social determinants of health, we lack the ability to collect and then use data in important ways.

It would be helpful for there to be a common form for data capture of demographic (and, then, non-demographic) data. And it would be helpful for the data to be presented in a common format with common definitions (e.g., dates are arranged by year, month, and day in one common format: YYYY/MM/DD or MM/DD/YYYY or DD/MM/YYYY). It matters not which form is chosen, so long as only one is chosen and then universally adopted. Sponsors and investigators should commit to annotating data with rich metadata. These simple measures would render data interoperable without the significant effort that data harmonization "at the back end" requires.

Importantly, collecting robust data in whatever granularity is possible or useful must then be stored, reported, and made available thereafter, accounting for the protections of privacy and confidentiality. Insofar as subgroups must be pooled (e.g., age brackets), the ranges chosen should be as informative as possible for the research question. In other words, if the study question involves treatments for prostate cancer, delineating pediatric populations would be pointless but segregating decadal age over the age of 50 might be important; if the study involves treatments for cystic fibrosis, then knowing whether the participant is an infant, child, young adult, adolescent, or adult might correlate with efficacy, particularly if patient cooperation in medication administration is necessary. The more these categories are common, and if not common, well defined, coupled with data definitions and robust meta-data, the easier it is to compare results across studies or to combine data in a meta-analysis.

Just as clinical research is a global endeavor, diversity and inclusion in clinical research requires global commitment and collaboration. Cooperation, accountability, and alignment among stakeholders are necessary. Further, cultural sensitivities change over time, and society and expectations are changing. We must remain responsive, respectful, attentive, and thoughtful. While we need to remain open to change, we must be vigilant to diverse representation and

inclusion as foundational to good science and to health equity, not only as a social good, but as a social necessity.

Part G – Appendix

Appendix 1: Abbreviations

ABCG2	ATP-binding cassette sub-family G member 2
A-HeFT	African American Heart Failure Trial
ACE	Angiotensin converting enzyme
ACP	Accelerated Cure Project
ACS	Acute coronary syndrome
ADME	Absorption, distribution, metabolism, and excretion
ALLHAT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attach Trial
ASCCEG	Australian Standard Classification of Cultural and Ethnic Groups
ASCO	American Society for Clinical Oncology
BLA	Biologics license application
BRCA	BReast CAncer gene
BMI	Body mass index
CBPR	Community-based participatory research
CDASH	Clinical Data Acquisition Standards Harmonization
CDER	U.S. FDA Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CF	Cystic fibrosis
CFR	Code of (U.S.) Federal Regulations
CFTR	Cystic fibrosis transmembrane conductance regulator
CHD	Coronary heart disease
CIOMS	Council for International Organizations of Medical Sciences
CISCRP	Center for Information and Study on Clinical Research Participation
CRF	Case report form
CRO	Contract research organization
CSR	Corporate social responsibility
CT	Controlled terminology
CTSU	Cancer Trials Support Unit
CVD	Cardiovascular disease
CYP	Cytochrome P450
CYP2C9	Cytochrome P450 2C9

CYP2C19	Cytochrome P450 2C19
CYP2D6	Cytochrome P450 2D6
DMC	Data monitoring committee
D&I	Diversity and Inclusion
EC	Ethics committee
EGFR	Epidermal growth factor receptor
EHR	Electronic health (medical) record
EMA	European Medicines Agency
ER	Estrogen receptor
ERN	Employee Resource Networks
EU	European Union
FAIR	Findable, Accessible, Interoperable, Reusable
FDA	U.S. Food and Drug Administration
FDARA	U.S. Food and Drug Reauthorization Act of 2017
FDASIA	U.S. Food and Drug Administration Safety and Innovation Act of 2012
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good clinical practice
GDPR	General Data Protection Regulation in the EU
GFR	Glomerular Filtration Rate
GOF	Gain-of-function
GRACE	Gender, Race and Clinical Experience study
HCP	Healthcare provider
HCV	Hepatitis C Virus
HDL	High-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human leukocyte antigen
HRA	Health regulatory authority
HTE	Heterogeneity of treatment effect
IL28B	Interleukin 28B
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH GCP	E6(R2) Guideline for Good Clinical Practice
ICF	Informed consent form
IND	Investigational new drug

IOM	Institute of Medicine (now National Academy of Medicine)
IPD	Individual patient-level data
IRB	Institutional Review Board
KPI	Key performance indicator
LACRC	Latin American Cancer Research Coalition
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LMIC	Low- and middle-income countries
LOF	Loss-of-function
MI	Myocardial infarction
MRCT	Multi-regional clinical trials
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCI	U.S. National Cancer Institute, NIH
NCT	National Clinical Trials (identifier number)
NDA	New drug application
NEP	Neutral endopeptidase
NGO	Non-governmental organization
NHLBI	U.S. National Heart, Lung, and Blood Institute, NIH
NIH	U.S. National Institutes of Health
NME	New molecular entity
OMB	U.S. Office of Management and Budget
PCORI	Patient-Centered Outcomes Research Institute
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamics
PI	Principal investigator
PK	Pharmacokinetics
PM	Poor metabolizer
PLATO	Platelet Inhibition and Patient Outcomes
PMC	Post-marketing commitment
PMDA	Japan's Pharmaceuticals and Medical Devices Agency
PMR	Post-marketing requirement
PR	Progesterone receptor
PRAPARE	Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences

PRIDE	Programs to Increase Diversity Among Individuals Engaged in Health-Related Research
PRO	Patient reported outcomes
PSP	Priority Setting Partnership
RCT	Randomized clinical trial
REC	Regulatory ethics committee
RSD	Recruitment strategy document
RWD	Real world data
RWE	Real world evidence
R&D	Research and development
SAGER	Sex and Gender Equity in Research
SDH	Social determinants of health
SES	Socio-economic status
SGM	Sexual and gender minority
sCR	Serum creatinine
TNBC	Triple negative breast cancer
WHO	World Health Organization
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform
WISE	Wisdom is Simply Exploration study
YCCI	Yale Center for Clinical Investigation

Appendix 2: Terminology and Definitions

Note: For terms relating to race and ethnicity as used in this document, please see separate Appendix 3.

Access: Access refers to the ability, right, or permission of an individual to use a service, resource, or object and implies the removal of barriers to allow such use.

Adaptive clinical trial: A clinical trial that evaluates a medical device or treatment by observing participant outcomes and possibly other measures (e.g., safety events) on a prescribed schedule, and modifying parameters of the trial protocol in accord with those observations. An adaptive design may reduce the total number of participants necessary in a trial, and it may be quicker and provide more flexibility than traditional clinical trials.

Adaptive design: A study that allows modifications to the clinical trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity.

ADME: An abbreviation used in pharmacology and pharmacokinetics for "absorption, distribution, metabolism, and excretion," that describes the drug disposition in an organism, each of which influence drug levels, kinetics, and thus safety and efficacy.

Allele: Any of several forms of a gene, usually arising through mutation, that are responsible for hereditary variation.

Availability: Availability refers to the presence of a service, resource, or object in an intended place and time, while access refers to its use of by an individual.

> **Relationship between access and availability:** Since the presence of a service, resource, or object is a necessary condition for use of that object, barriers to availability are important barriers to access. However, ensuring availability does not necessarily imply granting access for all relevant individuals. Consequently, an investigational medicine might be available in a place, but other barriers (e.g., ability to pay) may preclude an individual participant from having access to it.

Background regimen or background therapy: "Background regimen" or "background therapy" are terms used to denote required additional medications or treatments that are necessary for the effective use of the investigational medicine. Typically, background therapy will be considered in the potential future labeling of the product. For instance, an anti-infective (e.g., anti-HIV) agent may only be considered as a component of combination therapy; an anti-diabetic agent may only be tested in combination with a baseline drug (e.g., Metformin). Background therapy, in this context, does not include medications or other treatments for the participant unrelated to the investigational medicine or indication being tested.

Belmont Report:[605] A report, issued in 1978, published in 1979, and created by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, that summarizes ethical principles and guidelines for research involving human participants. Three core principles were identified: (1) respect for persons, (2) beneficence, and (3) justice. Three primary areas of application were also stated: (1) informed consent, (2) assessment of risks and benefits, and (3) selection of subjects.

Biological determinant: A biological factor that impacts health, typically classified as either endogenous (intrinsic) or exogenous (extrinsic). Examples of endogenous biological determinants include genetic ancestry, heritage, HIV status, health status, immunity, body mass index, age, race, and ethnicity. Examples of exogenous biological determinants include smoking status, alcohol consumption, diet, prescription and other drug use, and microorganisms that inhabit human beings.

Case Report Form: A paper or electronic form or questionnaire used by the sponsor of the clinical trial to collect data from each participant during the trial.

Chronic disease: The U.S. National Center for Health Statistics defines a chronic disease as one lasting three months or more that generally cannot be cured by medication and does not spontaneously remit.[606] The U.S. Department of Health and Human Services defines a chronic

[605] U.S. Department of Health and Human Services. The Belmont report: Ethical principles and guidelines for the protection of human subjects of research. US Department of Health and Human Services. 1979 Apr 18.
[606] Goodman RA, Posner SF, Huang ES, Parekh AK, Koh HK. Peer reviewed: defining and measuring chronic conditions: imperatives for research, policy, program, and practice. Preventing chronic disease. 2013;10.

condition as one that lasts a year or more and requires ongoing medical attention and/or limits activities of daily living.[607] Definitions of chronic disease vary widely in several aspects including duration or latency, disease nature, ability to cure, or functional limitation.[608]

Clinical trial: Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate safety and the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical or radiological procedures, devices, behavioral treatments, changes in clinical care, preventive care, etc. A **randomized clinical trial** prospectively assigns human participants to one of two or more groups by chance. We use the term *clinical trial* to refer to interventional studies involving volunteer participants.

Clinical research: The study of people, either through direct interaction or through the collection and analysis of data, blood, tissues, or other samples, to advance medical knowledge. Clinical research includes clinical trials but also other forms of research with human data and specimens.

Clinicaltrials.gov: A web-based resource that provides patients, their family members, health care professionals, researchers and the public with easy access to information and results database of publicly and privately supported clinical studies of human participants conducted around the world, hosted by the United States government (www.clinicaltrials.gov). Note that additional registries exist as well.

Demographic factors: Factors used to define the characteristics of a person or a population. The characteristics of a **person** typically include age, sex, level of education, amount of income, marital status, occupation, religion, etc. The characteristics of a **population** include average income, birth rate, death rate, the average size of a family, the average age at marriage, etc.

[607] Goodman RA, Posner SF, Huang ES, Parekh AK, Koh HK. Peer reviewed: defining and measuring chronic conditions: imperatives for research, policy, program, and practice. Preventing chronic disease. 2013;10.
[608] Goodman RA, Posner SF, Huang ES, Parekh AK, Koh HK. Peer reviewed: defining and measuring chronic conditions: imperatives for research, policy, program, and practice. Preventing chronic disease. 2013;10.

Drug: A substance recognized by an official pharmacopoeia or formulary, intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. The substance is intended for use as a component of a medicine but not a device or a component, part or accessory of a device.[609] Biological products are included in this definition. (See also **Medicinal Product**, the term used by the EMA.)

Effect size: A statistical concept that measures the strength of the relationship between two variables on a numeric scale.

European Federation of Pharmaceutical Industries and Associations (EFPIA):[610] A trade group that represents the biopharmaceutical industry operating in Europe. This association is the European counterpart to PhRMA (Pharmaceutical Research Manufacturers of America).

European Medicines Agency (EMA):[611] A decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. This agency is the EU counterpart to the U.S. FDA (Food and Drug Administration).

Ethnicity: A category of people who identify with each other, usually on the basis of presumed similarities such as common language, ancestry, history, society, culture, practices, beliefs, or nation.

EudraCT: European Clinical Trials Database that makes summary clinical trial results publicly available, hosted by the European Medicines Agency.

Feasibility assessment: An assessment of the practicality of a clinical trial, based on an objective evaluation of the strengths and weaknesses of the proposed site, including patient population to determine capacity and speed of enrollment, referral networks, investigator/site interest and experience in conducting similar trials, availability of qualified site personnel and facilities necessary to conduct the trial, patient recruitment techniques, and assessment of past enrollment and retention in similar studies, among others.

---

[609] U.S. Food and Drug Administration. Drugs@FDA Glossary of Terms. Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms [Accessed 18 July 2020]
[610] For more information, see https://www.efpia.eu/
[611] For more information, see https://www.ema.europa.eu

FDA (Food and Drug Administration):[612] The Food and Drug Administration is a federal agency within the United States Department of Health and Human Services, responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of the United States' food supply, cosmetics, and products that emit radiation. FDA also has responsibility for regulating the manufacturing, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.

Gender: The roles, behaviours, activities, attributes and culture typically associated with one's sexual identification. Gender interacts with, but is different from, the binary categories of biological sex.

Genetic ancestry: A way of describing family origins from geographic locations.

Genetics: The study of heredity.

Genome: The set of chromosomes that contains all the inheritable traits of an organism.

Genomics: The study of genes and their functions and related techniques.

Geographic ancestry: A way of quantifying a person's ancestral background statistically by understanding the history of a genome.

Health equity: The absence of avoidable, unfair, or remediable differences among groups of people, whether those groups are defined socially, economically, demographically or geographically or by other means of stratification. "Health equity" or "equity in health" implies that ideally everyone should have a fair opportunity to attain their full health potential and that no one should be disadvantaged from achieving this potential.[613]

Health literacy (U.S.): The degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate decisions. (Note:

[612] For more information, see https://www.FDA.gov
[613] World Health Organization. Health Equity. Retrieved from https://www.who.int/topics/health_equity/en/ [Accessed 20 October 2019]

Low health literacy can affect people of all ages, races, incomes, and education levels). Although health literacy is commonly defined as an individual trait, it does not depend on the skills of individuals alone. Health literacy is the product of the interaction between individuals' capacities and the health literacy-related demands and complexities of the health care system.[614]

Health literacy (Europe): The capacity to make sound health decisions in the context of everyday life – at home, in the community, at the workplace, in the healthcare system, in the marketplace, and in the political arena.[615]

Heterogeneity of treatment effect (HTE): The nonrandom, explainable variability in the direction and magnitude of treatment outcomes for individuals within a population. HTE is distinguished from random variability.

Informed consent (IC) or informed consent form (ICF): A document that has been reviewed and approved by the IRB/REC that is signed by the consenting investigator and research participant delineating potential risks and costs associated with participation in the clinical trial.

Institutional Review Board (IRB): A formally designated established committee to protect the rights and welfare of human research participants recruited to participate in research activities conducted under the auspices of the organization with which it is affiliated. The Institutional Review Board has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction. Further, it is responsible for monitoring the conduct of a trial. Also termed a research ethics committee (REC).

Intersectionality: The interconnected nature of categorizations such as race, class, and gender as they apply to a given individual or group, regarded as creating overlapping and interdependent systems of discrimination or disadvantage.

[614] U.S. Department of Health and Human Services (HHS). Office of Disease Prevention and Health Promotion. (2010). *National Action Plan to Improve Health Literacy.* Washington, DC: Author. 2010.
[615] European Patients Forum. Health Literacy. Retrieved from http://www.eu-patient.eu/whatwedo/Policy/Health-Literacy/ (Accessed 31 May, 2020).

Investigational new drug (IND): An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application.[616] Also termed **investigational medicinal product** (IMP) in the UK and elsewhere.

Investigational new drug application (NDA): The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S.[617]

Investigator: (see Sponsor-Investigator)

Investigational medicine: An investigational product that is a drug, biologic or biosimilar. Investigational medicines have not been approved by the cognizant national regulatory agency and are used or tested as a reference in a clinical trial. This definition includes a product with a marketing authorization that is used for an unapproved indication or in a way that is different from its approved form.

Investigational product: A preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used in a clinical trial. An investigational medicine may be an unlicensed product or a licensed product when used or assembled (formulated or packaged) differently from the approved form or when used for an unapproved indication or when used to gain further information about the authorized form.[618]

---

[616] U.S. Food and Drug Administration. Investigational New Drug (IND) or Device Exemption (IDE) Process (CBER). Available at: https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/investigational-new-drug-ind-or-device-exemption-ide-process-cber#:~:text=An%20Investigational%20New%20Drug%20Application,or%20biological%20product%20to%20humans. [Accessed 15 July 2020].

[617] U.S. Food and Drug Administration. New Drug Application. Available at: https://www.fda.gov/drugs/types-applications/new-drug-application-nda#:~:text=The%20NDA%20application%20is%20the,become%20part%20of%20the%20NDA. [Accessed on 15 July 2020].

[618] National Institute of Allergy and Infectious Diseases (NIAID). Investigational Product. Last reviewed on March 14,2013. Available at: https://www.niaid.nih.gov/research/dmid-investigational-product. [Accessed 31 May 2020].

Medicinal Product: A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action[619] (see also **Drug**, used by the FDA).

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

Multiplicity (or multiple testing): When multiple tests of hypotheses are performed within one randomized clinical trial, the likelihood that there will be an increase in the risk of a false positive is increased. If, for instance, one accepts a significance level of p=0.05 (a 5% error rate or 1 in 20 tests may be falsely positive), but one performs 5 tests on the same dataset, the likelihood that one of those five will be falsely positive increases to 23% ("5 shots on goal, not one"). Statistical adjustments must be made for multiple testing.

Non-demographic factors: Characteristics of a population such as socioeconomic factors, lifestyle patterns, environmental considerations (e.g., sunlight, pollution, housing density), language, compliance with medications, and other structural factors (e.g., access to health care).

Numeracy: The ability to use basic probability and mathematical concepts to explain mathematical and statistical terms. Numeracy principles in health literacy focus on simple explanations, instead of using complex fractions, percentages or statistical terms.

Participant: As used in this document, a person who enrolls in a clinical trial. Regulatory language and some other documents (e.g., the Belmont Report) refer to participants as "human subjects" or simply "subjects." "Participant" is used to denote potential and enrolled individuals as well as those who have completed their course of participation in a trial. If a specific subgroup of participants is intended, the term participant is appropriately modified (e.g., pediatric participants).

[619] European Medicines Agency. Available at: https://www.ema.europa.eu/en/glossary/medicinal-product. Accessed 18 July 2020].

Pharmacodynamics (PD): The study of a pharmacological or clinical effects of the medicine in individuals to describe the relation of the effect to dose or drug concentration. A pharmacodynamic effect can be a potentially adverse effect (anticholinergic effect with a tricyclic), a measure of activity thought related to clinical benefit (various measures of beta-blockade, effect on ECG intervals, inhibition of ACE or of angiotensin I or II response), a short term desired effect, often a surrogate endpoint (blood pressure, cholesterol), or the ultimate intended clinical benefit (effects on pain, depression, sudden death). [620]

Pharmacokinetics (PK): The study of how a medicine is handled by the body, usually involving measurement of blood concentrations of drug and its metabolite(s) (sometimes concentrations in urine or tissues) as a function of time. Pharmacokinetic studies are used to characterize absorption, distribution, metabolism and excretion of a drug, either in blood or in other pertinent locations (e.g., cerebral spinal fluid). When combined with pharmacodynamic measures (a PK/PD study) it can characterize the relation of blood concentrations to the extent and timing of pharmacodynamic effects.

Phase of trial: Interventional biomedical clinical trials of experimental drugs, treatments, devices, vaccines, or behavioral interventions may proceed through four phases:[621]

1. Phase 1: Clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
2. Phase 2: Clinical trials study the biomedical or behavioral intervention in a larger group of people (often several hundred) to determine preliminary efficacy and to further evaluate its safety.
3. Phase 3: Studies investigate the efficacy of the biomedical or behavioral intervention in large groups of participants (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

[620] Definitions of pharmacokinetics, pharmacodynamics, and therapeutic dose range are derived from ICH E5 (R1).
[621] Adapted from: https://www.fda.gov/patients/clinical-trials-what-patients-need-know/what-are-different-types-clinical-research

4. Phase 4: Studies are conducted after the intervention has been marketed (post-marketing studies). These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

Pragmatic clinical trial: A clinical trial that focuses on correlation between treatments and outcomes in real world health systems and practice, rather than on proving causation.

Predictive modeling: A process that uses data mining and probability to forecast outcomes. Each model is composed of predictors or variables that are likely to influence future results. Using these predictors, a statistical model is formulated.

Race: A grouping of humans based on shared physical or social qualities into categories generally viewed as distinct by society.

Rare disease: A disorder or condition that affects fewer than 200,000 people in the U.S.[622] In its definition, the EU also incorporates some tropical diseases that are primarily found in developing nations.

Research Ethics Committee (REC): A formally designated committee to monitor, review and approve biomedical and behavior research involving human participants. REC (and sometimes simply Ethics Committee [EC]) is often the preferred term in Europe, Africa, and Asia. Also termed an IRB.

Reflexivity: "A technique used in qualitative research [that] calls on the researcher to explore personal beliefs in order to be more aware of potential judgments that can occur during data collection and analysis."[623]

Serious disease or condition: The U.S. Food and Drug Administration (FDA) defines a serious disease or condition as "... a disease or condition associated with morbidity that has substantial

[622] Public Law 97-114, 97th Congress of the United States. The Orphan Drug Act. Enacted Jan 4, 1983 [H.R. 5238] Available at https://www.fda.gov/media/99546/download. [Accessed 31 May 2020].
[623] Yeager KA, Bauer-Wu S. Cultural humility: essential foundation for clinical researchers. Appl Nurs Res. 2013 Nov;26(4):251-6. doi: 10.1016/j.apnr.2013.06.008. Epub 2013 Aug 12. PMID: 23938129; PMCID: PMC3834043.

impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."[624]

Sex: The phenotypic expression of chromosomal makeup at birth that defines an individual as male, female, or other.

Sexual and gender minority (SGM): "SGM populations include, but are not limited to, individuals who identify as lesbian, gay, bisexual, asexual, transgender, two-spirit, queer, and/or intersex. Individuals with same-sex or -gender attractions or behaviors and those with a difference in sex development are also included. These populations also encompass those who do not self-identify with one of these terms but whose sexual orientation, gender identity or expression, or reproductive development is characterized by non-binary constructs of sexual orientation, gender, and/or sex."[625]

Social determinants of health: The economic and social conditions that influence individual and group differences in health status, including one's living and working conditions (e.g., income, wealth, influence, and power), rather than individual risk factors (e.g., genetics, behaviors) that influence the risk for or vulnerability to a disease or injury.

Sponsor investigator: Also called the Principal Investigator (PI) who holds the investigational new drug application (IND). Sponsor-investigator is also defined as the person who both initiates and conducts the clinical study.

[624] United States Food and Drug Administration, 2015b, 21 C.F.R. § 312.300b1 Investigational New Drug Application. Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.300. [Accessed 31 May 2020].
[625] Sexual and Gender Minority Populations in NIH-Supported Research. Notice number NOT-OD-19-139, Release date August 28, 2019. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-139.html.

Stakeholder: "A person or group with an interest or concern in something; one who is involved in or affected by a course of action."[626]

Standard of care: A diagnostic and treatment process that a clinician should follow for a certain type of patient, illness, or clinical circumstance. In legal terms, the level at which the average, prudent provider in a given community would practice. It is how similarly qualified practitioners would have managed the patient's care under the same or similar circumstances.[627]

Stratification: The categorization of groups based on certain intrinsic or extrinsic factors (e.g., age, sex, gender, race, ethnicity, wealth, income, education, occupation, and social status).

Subgroup: The subdivision of a group, often secondary to differences in intrinsic or extrinsic characteristics, practices, beliefs, or conduct.

Subgroup analysis: A type of analysis done by breaking down study samples into subsets of participants based on a shared characteristic in order to explore differences in how people respond to an intervention.

Subject: A term used in U.S. regulations to indicate a human participant in a clinical trial. In this document, the term "participant" is used to more accurately state the relationship between those who create and conduct research, and those who enroll in clinical trials.[628]

Therapeutic dose range: The difference between the lowest effective dose and the highest dose that gives further benefit.

Therapeutic window: The range of doses that produces a therapeutic response without causing significant adverse effects in individuals (i.e., the doses that provide efficacy without unacceptable toxicity).

[626] Dictionary.com, 2016
[627] MedicineNet, 2016.
[628] Boynton PM. People should participate in, not be subjects of, research. Bmj. 1998 Nov 28;317(7171):1521.

> **Narrow therapeutic index** drugs: "Drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity."[629]

Trial participant: Also called study participant, research subject, study participant, and clinical trial participant. This is the individual who participates in the clinical trial.

Trial results: For the purpose of this document, trial results encompass a description of summary trial results, by study arm, study arm information, clinical plan or milestone information that is relevant to participants.

Type I error: The rejection of a true null hypothesis (also known as a "false positive").

Type II error: The non-rejection (or acceptance) of a false null hypothesis (also known as a "false negative").

Unmet medical need: The U.S. FDA defines "unmet medical need" as "a condition whose treatment or diagnosis is not addressed adequately by available therapy."[630] This condition includes an immediate need or a long-term need for a population or society. Similarly, unmet medical need is defined by the European Parliament and the Council as "a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorized in the community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected."[631]

[629] FDA , 2015. Regulatory Science Research Report: Narrow Therapeutic Index Drugs (Version 9 May 2017). See https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2015-regulatory-science-research-report-narrow-therapeutic-index-drugs [Accessed 25 March 2020]

[630] U.S. Food and Drug Administration. Guidance for industry: expedited programs for serious conditions—drugs and biologics. Silver Spring, MD: US Food and Drug Administration. 2014 May 20.

[631] European Commission. Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council. Official Journal of the European Union. 2006;50:6-9.

Appendix 3: Terminology for Race used in this Document

There are many categorizations and differing definitions of race and ethnicity, and no single interpretation of a category is sufficient to describe the complexity and sensitivities embedded in their use. Further, these terms are highly personal, and categories are often not discrete. What is important is how individuals self-identify and that respect for those identities and individual dignity be preserved.

There is no one correct categorization. Therefore, in this document we have used the terms as currently presented by the U.S. Office of Management and Budget (OMB)[632] to simplify and standardize terms of use. In doing so, we realize that the decision is "U.S.-centric" and that other countries have different designations and categories; we respect that these terms are location- and region-specific and may not apply, but we needed to choose established terms to use in order to maintain a focus on inclusion and equity in clinical research and not on the terms themselves. OMB states, and we agree that, "the racial and ethnic categories set forth in the standard should not be interpreted as being scientific or anthropological in nature."[633] Importantly, OMB specifies that a *minimum* of five categories will be used for reporting data on race, and two categories for reporting data on ethnicity, thereby acknowledging that additional categories exist.[634] We also note that certain parts of the policy directive are currently under

[632] Federal Register. Office of Management and Budget. Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity. Vol 62, No 210. 58782-58790. October 30, 1997. Available at: https://www.govinfo.gov/content/pkg/FR-1997-10-30/pdf/97-28653.pdf [Accessed 24 May 2020]
[633] Federal Register. Office of Management and Budget. Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity. Vol 81, No 190. 67398-67401. September 30, 2016. Available at: https://www.govinfo.gov/content/pkg/FR-2016-09-30/pdf/2016-23672.pdf [Accessed 24 May 2020]
[634] Notably, OMB states "The categories should set forth a minimum standard; additional categories should be permitted provided they can be aggregated to the standard categories," thereby suggesting that the additional categories should "roll up" to one of the five designated categories. Federal Register. Office of Management and Budget. Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity. Vol 81, No 190. 67398-67401. September 30, 2016. Available at: https://www.govinfo.gov/content/pkg/FR-2016-09-30/pdf/2016-23672.pdf [Accessed 24 May 2020]

review by OMB.[635] We welcome the planned revision and will revise this document from time to time as terms evolve.

American Indian or Alaska Native: "A person having origins in any of the original peoples of North or South America (including Central America), and who maintains tribal affiliation or community attachment."[636]

Asian: "A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam."[637]

Black or African American: "A person having origins in any of the black racial groups of Africa."[638] *Note*: The term Black is used in this guidance instead of "Black or African American." In this document, whenever a publication has used the term "Black or African American" as a self-defined race category (e.g., in reporting study results), we have retained the designation.

Hispanic or Latino: "A person of Cuban, Mexican, Puerto Rican, Cuban, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."[639]
Note: The term Hispanic is most commonly used in the U.S.. Latino or Latina are alternative designations that emphasize Latin American descent. Outside the U.S., individuals generally self-identify as being from their country of origin.

White: "A person having origins in any of the original peoples of Europe, the Middle East, or North Africa."[640]

---

[635] Federal Register. Office of Management and Budget. Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity. Vol 81, No 190. 67398-67401. September 30, 2016. Available at: https://www.govinfo.gov/content/pkg/FR-2016-09-30/pdf/2016-23672.pdf [Accessed 24 May 2020]
[636] Federal Register. Office of Management and Budget. Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity. Vol 62, No 210. 58782-58790. October 30, 1997. Available at: https://www.govinfo.gov/content/pkg/FR-1997-10-30/pdf/97-28653.pdf [Accessed 24 May 2020]
[637] Ibid.
[638] Ibid.
[639] Ibid.
[640] Ibid.

Note: Outside the U.S., national ancestry has largely replaced the concept of race, and white is often used as an adjective to describe subgroups of a national heritage (e.g., white South Africans).

Additional comments:

The following terms are not used in the most recent OMB guidance but have been used in this document and are therefore described:

Caucasian: A person native to the Caucasus region, an area situated between the Black Sea and the Caspian Sea and mainly occupied by Armenia, Azerbaijan, Georgia, and Russia. The term has been adapted and used to describe individuals who trace their ancestry to Europe. We have used this term only if a publication has used the term to define the population.

Latinx: Latinx (or LatinX) is a gender-neutral term that may be used instead of Latino or Latina to refer to people of Latin American cultural or ethnic identity. We have used this term if a publication has used the term to define the population.