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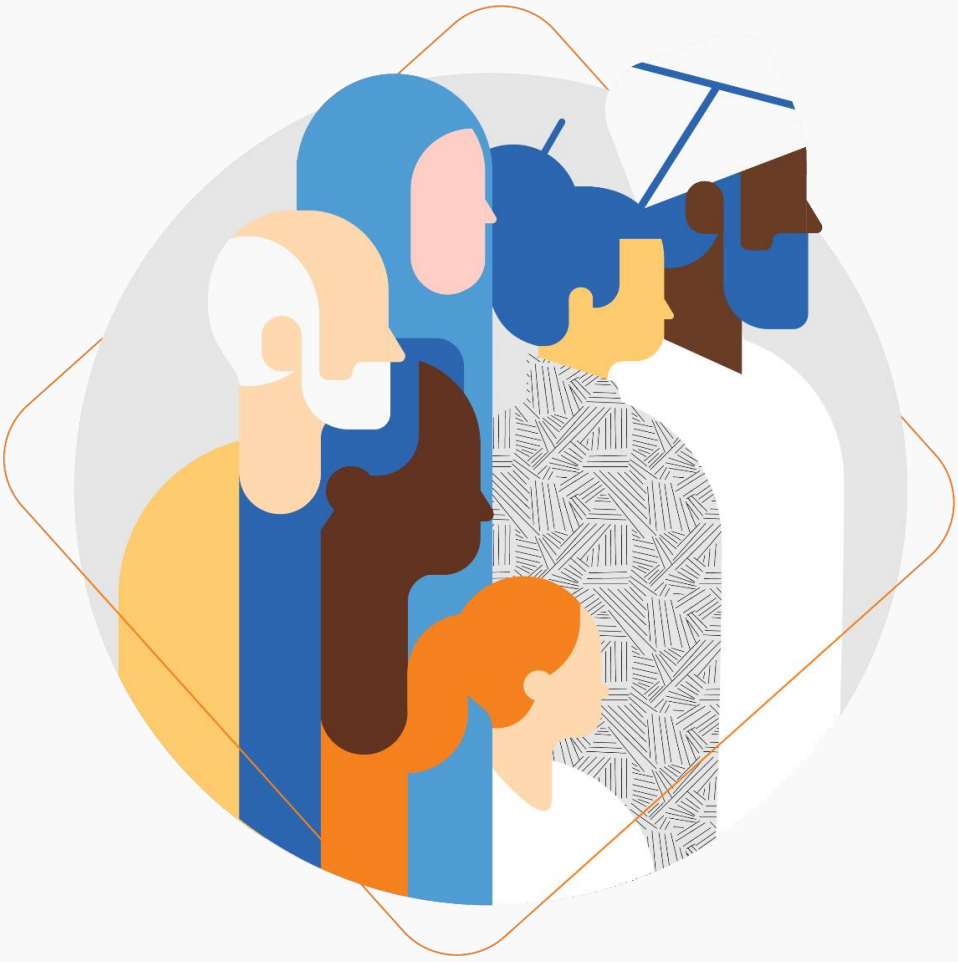
Achieving diversity, equity and inclusion in clinical trials



An in-depth look at understanding and overcoming barriers to patient participation

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1. Introduction

The prevalence of communicable and non-communicable diseases are increasing worldwide, placing considerable demand on public health systems and driving a necessity to develop more effective targeted therapies. This is reflected in the exponential growth of registered clinical trials in the last two decades – from 2,673 in 1999, to 600,713 in 2020.[1] Clinical trials are the cornerstone of *precision medicine* and are not possible without the volunteers who take part. As defined by the US National Institutes of Health (NIH), precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."[2] By considering this variability, the core of executing precision medicine is collecting data from a diverse study population representing real-word patients. However, despite growing initiatives and practices to make trials more patient-centric and representative of today's societies, most studies still fail to enroll inclusive and diverse patient populations. To illustrate, in 2020, minority racial/ethnic groups represented only 25% of patients in clinical trials,[3] despite comprising 40% of the US population[4] – limiting the generalizability and applicability of new treatments in underrepresented groups. Furthermore, this lack of diversity contributes towards growing social and health disparities, particularly among underrepresented, underserved, and minority populations who tend to bear the unbalanced brunt of some of the most common conditions and diseases (e.g., diabetes, cardiovascular disease, etc.). To improve social and health equity for everyone, the clinical trial research industry first needs to ensure that medicines and therapies are effective in the patients who need them most. This requires a nuanced and targeted approach to understand who these patients are.

Furthermore, medicines approved in the US prior to the NIH Revitalization Act in 1993 were predominantly tested in "single, white men."[5] This glaring omission of other patient populations when developing medicine and therapies, has led to sometimes fatal outcomes in other racial/ethnic groups, as well as in women. For example, warfarin (a commonly used anticoagulant to treat blood clots) was discovered to have higher rates of adverse events and even death in Black/African or Hispanic/Latino patients.[6] Yet, of 12 prospective randomized trials on warfarin, 80% of study participants were white. Furthermore, between 1997-2000, a shocking 8 out of 10 drugs were removed from the US market as they caused severe side effects or led to fatalities in women.[7] Unfortunately, because clinical trials were historically less inclusive, responses to treatments by different patient groups were only discovered retroactively and after a substantial accumulation of adverse events. In recognition of the need to overcome disparities in health outcomes, several regulatory bodies recently created guidelines on how to enroll more diverse

patient populations. These include guidelines by the US FDA on "Enhancing the Diversity of Clinical Trial Populations" (Nov 2020)[8] and the "Collection of Race and Ethnicity Data in Clinical Trials" (Oct 2016)[9]; the NIH policy on the "Inclusion of Women and Minorities as Subjects in Clinical Research" (Nov 2017)[10] in NIH-funded research; and the European Association of Science Editors' "Sex and Gender Equity in Research Guidelines" (May 2016).[11] More recently, as minority communities were more severely affected by the COVID-19 pandemic, the US FDA issued recommendations in their guidance document, "Development and Licensure of Vaccines to Prevent COVID-19" (June 2020), that encouraged the "enrollment of populations most affected by COVID-19, specifically racial and ethnic minorities."[12]

With growing evidence showing the need for precision medicine, trickle down effects to actual solutions have proven glacial, despite known risks in continuing this way. Consequently, the approach and pace is not justified from a scientific, ethical, or moral position. Following social movements such as Black Lives Matter and Stop AAPI (Asian American Pacific Islander) Hate – along with COVID-19 that compounded striking social inequalities – there is now an increasing call and opportunity for clinical trial stakeholders (e.g., sponsors, regulatory bodies, patient groups, research institutes) to take an energized approach towards advocating for and realizing diversity, equity, and inclusion (DEI) in clinical trials. This includes implementing regulatory guidelines (e.g., reporting diversity metrics); pushing for structural changes (e.g., hiring more diverse investigators and clinical staff); adapting study designs (e.g., decentralized methods and reevaluating inclusion/exclusion criteria); improving health literacy (e.g., creating accessible medical and study information) and communication (e.g., using layman terms and local languages); rebuilding trust (e.g., empathy and transparency); and being aware of the way that individual backgrounds shape trial interest, recruitment, and retention (e.g., intersectionality, cultural competency training).

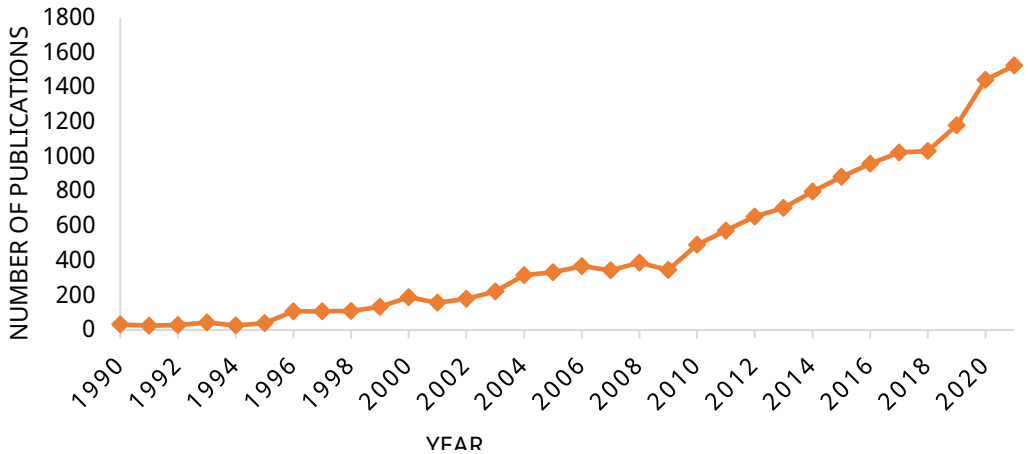
To gain a deeper understanding of how we can achieve diversity in clinical trials, we examine:

- **What is diversity?** How diversity is measured and how this term has evolved.
- **What are potential barriers patients face?** How different patient communities have been excluded in the past and challenges they still face today.
- **What are solutions to improving DEI in clinical trials?** Our general recommendations and group-specific measures.
- **How does Clariness fit in?** Our patient-centric approaches to DEI.
- **Our key takeaways.** Where we hope to go as an industry.

2. What is diversity?

Since the 1990s, publications addressing patient diversity in clinical trials have increased from a few hundred articles a year to almost 1,500 yearly articles[13] (**Figure 1**). Despite increasing awareness, many clinical trial stakeholders continue to struggle with creating a single useable definition of diversity in clinical trials and – let alone – developing a standardized process and set of measures on how to achieve diversity in clinical trials. To better understand this issue, we first need to understand how various experts have defined diversity in the context of clinical research in the past and how this term continues to evolve today.

Figure 1. Publications with ''diversity'' and ''clinical trials'' on PubMed.

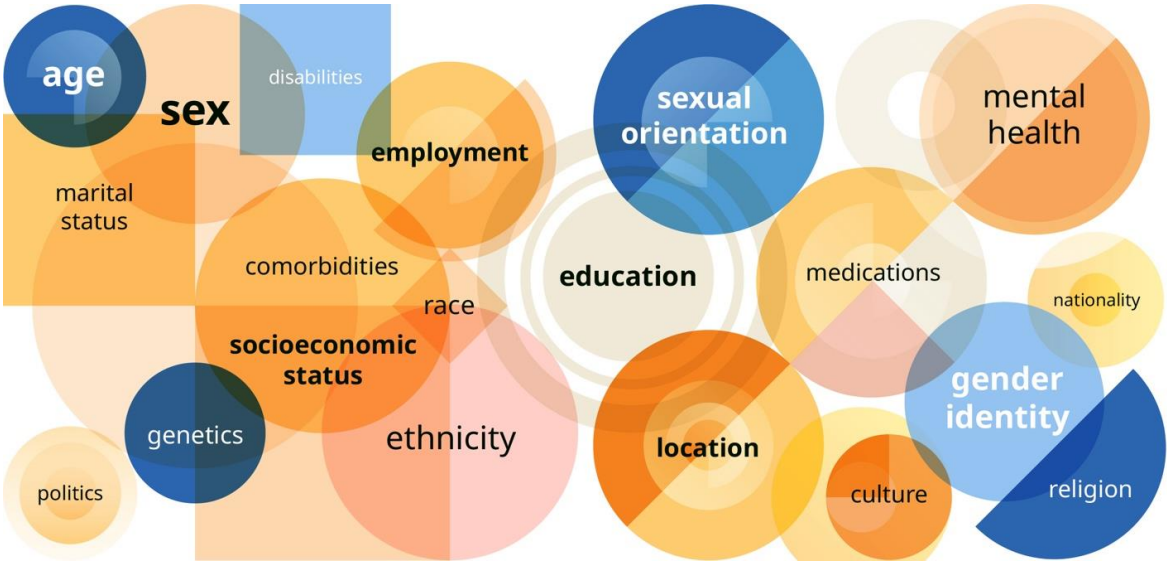


Number of publications mentioning “diversity” and “clinical trials” on PubMed between 1990-2020.[13]

2.1. Defining diversity in clinical trials

Most definitions of diversity in clinical research center around the “practice or quality of including or involving people from a range of different social and ethnic backgrounds and of different genders, sexual orientation, etc.”[14] Therefore, categorizing different backgrounds does not solely refer to the inclusion of a variety of racial/ethnic backgrounds, but also includes other demographic (e.g., sex, age, location of residence, socioeconomic status, etc.) and non-demographic (e.g., disabilities, comorbidities, genetics, concurrent medications, etc.) factors (**Figure 2**).[8,15]

Figure 2. Intersectionality: Different Dimensions of Diversity.



Individual identities are formed by overlapping demographic and non-demographic factors.

Before being able to create guidelines and steps towards improving diversity in clinical trials, it is important to first observe how diversity has been presented in two slightly different and nuanced ways:

1. **Diversity as representation:** In this concept, diversity focuses on ensuring that study populations reflect real-world compositions in society and/or specific patient populations in clinical trials.[16] This approach also considers barriers certain patients may disproportionately face when accessing clinical trials to ensure accurate representation when recruiting patients.[17,18]
2. **Diversity as improving clinical outcomes:** In this concept, diversity focuses on considering group-specific clinical outcomes and responses to treatment.[19] Therefore, diversity is not merely representing real-world compositions in society or specific patient populations, but also ensuring that new medicines and therapies are actually effective in these patient populations. This requires acknowledging that different patient groups display varying disease prevalence,[20] responses to treatment,[19,21] and requires additional considerations (e.g., social, environmental, biological, and genetic factors) that are not homogenous across all patients, indications, or patient communities.[19,22] Accordingly, it's not just about letting a homogenous study population represent real-world patient populations, but rather about

focusing on *group-specific differences* in clinical outcomes of medicines or therapies and discovering their true underlying mechanisms.[19]

To better understand the different implications of these two usages of diversity, we take a detailed look into examples of what this means in clinical practice.

2.2. Diversity as representation

Following the aphorism, "Your results are only as good as your data," diversity as representation primarily focuses on increasing the diversity of study populations in clinical trials to accurately represent real-world compositions in society and/or patient populations, thereby improving health equity by giving more equal access to specialized treatments and care. For example, Aldrighetti *et. al.* (2021)[23] recently performed a cross-sectional analysis on racial/ethnic disparities in breast, prostate, lung, and colorectal cancer precision medicine studies. They found that in 93 clinical trials with 5,867 participants, non-Hispanic white patients (82.3%) were overrepresented and minority groups underrepresented relative to US cancer incidence rates.[23] They concluded that to actually collect "meaningful precision data," oncology clinical trials need to include more representative patient populations to ensure that benefits of cancer research also apply to minority and underrepresented patients – especially since biomarker and genetic testing play a pivotal role in treatments.

A recent example on the importance of making trial populations representative of real-world patients was seen during the COVID-19 pandemic. The US government and health authorities released several statements urging sponsors of COVID-19 clinical trials to enroll those (i.e., racial and ethnic minorities) who were most impacted by the pandemic to ensure that vaccines were effective in and available to individuals from all backgrounds.[24,25] The urgency behind these statements became clear during the pandemic as certain communities (e.g., Black/African American and non-Hispanic white) were disproportionately affected by the virus (e.g., higher risk/rates of morbidity and mortality),[26] as well as during vaccine rollouts (e.g., lower vaccination rates, higher rates of concern over vaccines).[27] Key reasons for this stark imbalance in health equity stems primarily from historical inequality, (systemic) racism, discrimination, low medical trust among these communities, language and cultural barriers, socioeconomic status, types of employment (e.g., less flexibility and opportunities for remote work), health literacy, education, limited transportation options, as well as living in areas with worse access to hospitals.[26–32] Furthermore, some scientists argued, including Dr. Anthony Fauci (Director of the National

Institute for Allergy and Infectious Diseases in the US), that Black/African American and non-Hispanic white patients should even represent a slight majority of volunteers in COVID-19 vaccine clinical trials as these communities are disproportionately affected by the pandemic.[31,33]

This notion of diversity as representation thus looks at clinical trials (particularly during the patient recruitment process) with aims to create a more representative study population reflecting real-word patient communities. To improve participation of underrepresented or minority patients in clinical trials requires an intersectional approach (**Figure 2**) overcoming group-specific barriers and designing culturally appropriate outreach campaigns to these communities. However, this diversity metric is just one step towards DEI in clinical trials as it only accounts for one aspect of precision medicine and may not fully address how certain patient subpopulations are affected by a condition or how they respond to certain medicines or treatments.[19]

2.3. Diversity and clinical outcomes

Apart from diversity as representation, some clinical scientists push for diversity to go beyond merely creating a more diverse study population. Instead, they argue that diversity means fundamentally *redesigning* clinical trial protocols, hypotheses, and primary and secondary research objectives in a way that addresses group-specific clinical outcomes. For decades, Randomized Clinical Trials (RCTs) have been the "gold standard" in evidence-based medicine, ensuring that therapies are effective for all individuals.[19,34] However, this "requires that the hypotheses underlying studies based on a nuanced understanding of possible differences between groups should be studied in a population that represents groups that differ on the aspects considered to be relevant"[19] – meaning that it isn't just about including a diverse and representative patient population, but also addressing underlying biological/sociocultural mechanisms that are meaningful to those specific patient groups and leads to relevant clinical outcomes.

To improve DEI, sponsors (and clinical trial stakeholders) should be held accountable by reporting on diversity measures, as well as group-specific outcomes. However, to report these outcomes requires understanding to what extent subgroup analyses is required (i.e., if it provides meaningful clinical data), with a large enough sample size of different patient groups to perform subgroup analyses – which remains problematic as many trials still fail to meet diversity standards and do not (or are unable to) report any group-specific outcomes.[19,35] Additionally, certain results of (sub)group-specific analyses may also be misleading due to limited power and

small sample sizes that are unable to accurately detect any differences in efficacy or safety between patient groups.[36,37] Still, despite regulatory reforms calling for the enrollment of more diverse patient groups (e.g., NIH Revitalization Act in 1993), Stronks *et al.,* 2013 notes that "there is still little evidence on diversity in the efficacy of treatment, leading to a lack of diversity-sensitive guidelines for professionals."[19] These challenges only highlight the medical Catch-22 when trying to improve diversity and clinical outcomes in clinical trials, which, in part, requires targeted outreach to recruiting specific patient subgroups.

Box 1. Case study: The Women's Health Initiative.

A case study on initiatives that were inclusive and improved group-specific outcomes was the groundbreaking Women's Health Initiative (WHI) – a long-term national health study launched in 1991 to address cardiovascular disease, cancers, and osteoporotic fractures in postmenopausal women.[38,39] As one of the largest women's health projects in the US, the study enrolled >160,000 women (50-79 years old) across 40 clinical centers, with approximately 64,500 women participating in a randomized controlled clinical trial (CT) and 100,000 women in a complementary observational study (OS).[39]

The Women's Health Initiative Logo.

One of the key findings by the WHI was that hormone replacement therapy is not effective in preventing heart disease in postmenopausal women[40] – a finding in direct contrast to previous observational studies that suggested potential cardiovascular benefits.[41] Furthermore, hormone therapy with estrogen and progestin actually increased the risk of breast cancer, stroke, and myocardial infarction in postmenopausal women – leading to the US Food and Drug Administration to approve a labeling change, along with "a statement that hormone therapy should be considered only for women at significant risk of osteoporosis who cannot take nonestrogen medications."[41] Following this, a shift from estrogen to nonestrogen therapy was observed in osteoporosis treatments.[41]

The WHI also made efforts to enroll women from racial and ethnic minority groups, with a minority recruitment target set to 20% for both the CT and OS.[39] To achieve this, 10 out of 40 WHI clinical centers were minority recruitment centers due to "their history of interaction with and access to large numbers of women in at least one of the four targeted [racial/ethnic] groups."[42] The 30 remaining centers "were expected to recruit as many women from these historically underrepresented race and ethnicity groups as they could."[42] A cross-sectional analysis (using the baseline data from the WHI) later showed differences in lifetime morbidity burden among different racial/ethnic groups, with Black/African American or Native American/Alaska Native women more likely to have higher lifetime morbidity burden than white women.[43]

The knowledge gained from the WHI have continued to prove crucial in the persistent improvement of women's health and is estimated to have saved approximately "$35.2 billion in direct medical costs in the United States."[40] Additionally, the 2020–2021 WHI Race and Ethnicity Task Force more recently created the WHI Race and Ethnicity Language and Data Interpretation Guide that outlines recommendations on how to include race and ethnicity in methods, analyses, and reporting to ensure that clinical trials are inclusive and that clinical outcomes apply to all patient communities.[42]

2.4 Considerations and uses

In past decades, researchers from progressively interdisciplinary backgrounds have increasingly brought forth critiques on clinical research's conceptualization of diversity – arguing that it is often based on essentialist conceptions of race/ethnicity, gender, or other socially constructed identities.[42,44–46] According to these critiques, inconsistent, unclear, or misinformed methods of classifying patient subgroups can actually lead to barriers that may hinder recruitment efforts and lead to the continued medical distrust and miscommunication seen among certain minority populations today.[42,46]

These critiques focus on the following 2 points:

1. Identities are not "monolithic" or homogeneous: It has been criticized that during patient recruitment efforts, minority populations (e.g., racial/ethnic) are often treated as homogenous groups. For example, during the COVID-19 pandemic, media outlets, politicians and health officials used a singular example – the infamous Tuskegee Syphilis Study – to explain the apparent mistrust of all Black/African Americans towards medical institutions and the vaccines specificically.[47,48] This (highly unethical) infamous study was organized by the US Public Health Service (PHS) between 1932–72 to study the effects of untreated syphilis in Black/African American men.[49] However, Katz *et al.* (2008)[49] found that although Black/African Americans had more general awareness and knowledge of the Tuskegee study, they did not find this to be associated with their willingness to participate in biomedical research. Furthermore, researchers found that the majority of Black/African Americans have more "modern reasons" for hesitating. In other words: Tuskegee is often used as a "scapegoat" by health officials and politicians to avoid looking at deeper (modern) barriers to distrust in medical research.

> *"If you continue to use [Tuskegee] as a way of explaining why more African Americans are hesitant, it almost absolves you of having to learn more, do more, involve other people – admit that racism is actually a thing today."*[47] – Karen Lincoln, professor of social work at USC and founder of Advocates for African American Elders

Additionally, from a practical point of view, treating certain populations as homogenous based on a certain categorization is also inherently false when looking at responses to treatment. For

example, naltrexone (a medication used to treat substance abuse) showed different outcomes in Black/African American patients when stratified based on low or high West African genetic ancestry.[6] Although differences were found between Black/African American versus non-Hispanic white participants, Black/African American participants with low West African ancestry showed no measurable differences in response when compared to their non-Hispanic White counterparts.

2. Identities overlap and intersect: As is increasingly emphasized by scholars across all disciplines (from medicine, biology, social science, anthropology, history, and philosophy),[50–53] multiple "identities" (**Figure 2**) can coexist within one person and are fluid and evolve over time. Therefore, categorizing individuals under one identity is highly one-dimensional, limiting, and potentially exclusive. Understanding a variety of potential identities (or sense of *belonging* to a group) within the framework of "intersectionality" was first proposed by Kimberlé Crenshaw (1989)[50] when highlighting the discrimination or exclusion faced by Black/African American women relative to their gender and race. Since then, intersectionality has expanded to become a *"theoretical framework that posits that multiple social categories (e.g., race, ethnicity, gender, sexual orientation, socioeconomic status) intersect at the micro level of individual experience to reflect multiple interlocking systems of privilege and oppression at the macro, social-structural level (e.g., racism, sexism, heterosexism)."*[51]

For clinical trials, this means that diversity should be understood as being person- and context-dependent, i.e., that potential study participants are multidimensional and may self-identify and/or belong to different categories that expose them to different social/environmental factors that in turn affects their health, disease risk, and access or barriers to healthcare and treatments.[42,51,52]

To illustrate, the use of "women and minorities" is often used in public health discourse (e.g., in the NIH Revitalization act on the "inclusion of women and minorities in clinical research"[10]), which may imply these categories to be mutually exclusive and may hide that these two categories can intersect (e.g., Black women).[51] Additionally, the term minority is often used with race/ethnicity, but also applies to those in LGBTQIA+ communities, people with disabilities, as well as white Americans living in rural areas (i.e., underserved communities).[51] Therefore, improving DEI in clinical trials means considering all potential identities that may exist in different people as well as taking into account how this can affect their participation in clinical trials.

> *"Confronting diversity in clinical research starts with formulating hypotheses as to why diversity does or does not matter in a specific case"* – Stronks et al (2013)[19]

What these considerations all highlight is that a one-size-fits-all approach doesn't really fit if we want to achieve health equity and precision medicine. Indeed, as Stronks *et al* (2013)[19] also argues, "confronting diversity in clinical research starts with formulating hypotheses as to why diversity does or does not matter in a specific case" – and then developing different methodologies for recruitment, retention, data analyses, and reporting based on this knowledge. This means that every clinical study requires a thoughtful and nuanced understanding of patient populations, followed by a carefully targeted method on how to communicate with and reach specific populations.

Do you need support with improving DEI in your clinical studies? Contact Clariness here to learn more about how we can reach underrepresented patients.

3. What are potential barriers patients face?

As previously discussed, dimensions of diversity refer to a broad consideration of demographic (e.g., race/ethnicity, gender/sex, age, location of residence, socioeconomic status, etc.) and non-demographic (e.g., disabilities, comorbidities, genetics, concurrent medications, etc.) factors (**Figure 2**).[8,15] Within each dimension, individuals face unique barriers that also intersect with other dimensions, forming complex mosaics of social, economic, and health opportunities and outcomes for each individual. While clinical research has historically attempted to limit variability within study populations to control confounding factors, researchers are now increasingly aware that including a homogenous study population can mask underlying differences in responses between groups, while also biasing effective treatments towards a limited group.

These concerns led to the promotion of patient recruitment practices that could lead to the enrollment of more diverse and representative patient populations in clinical trials outlined in several guidance documents, including the US FDA's on "Enhancing the Diversity of Clinical Trial Populations,"[8] "Collection of Race and Ethnicity Data in Clinical Trials,"[9] and the more recent "Development and Licensure of Vaccines to Prevent COVID-19" (June 2020), that encouraged the

"enrollment of populations most affected by COVID-19, specifically racial and ethnic minorities."[12] Other guidelines include the NIH policy on the "Inclusion of Women and Minorities as Subjects in Clinical Research"[10] in NIH-funded research and the European Association of Science Editors' "Sex and Gender Equity in Research Guidelines."[11] To better understand what barriers patient communities may face, the National Institute of Minority Health and Health Disparities (NIMHD) in the US "congressionally mandated designated disparity groups"[54] which fall within:

- **Race and ethnicity**
- **Sex and gender**
- **Age**
- **Location** (e.g., underserved rural populations or certain urban neighborhoods)
- **Other social determinants less often or not reported at all** (e.g., access to care, disabilities, household income, education, etc.)

By exploring different demographic categories or dimensions that are essential for DEI in clinical trials, we can start to identify which groups are underrepresented and how to overcome the barriers they face.

3.1. Race and ethnicity

As the number of clinical trials continues to grow, having a study population that accurately represents real-world patient populations is a first step towards achieving health and social equity. To illustrate, in a recent analysis performed in 2020[55] on global clinical trial participants, 76% were white, 11% Asian, 7% Black, and 6% other; in contrast, 60% of the global population is Asian, 16% African, 10% European, 7% Latin American, and 7% other. This lack of diversity continues to hinder social progress by limiting the applicability of treatments as recent studies show that treatments may work differently among various patient groups. For example, Ramamoorthy *et al.* (2015)[56] analyzed 167 new molecule-based therapies and found that 1 in 5 new medications approved in the previous 6 years showed different responses across several racial/ethnic groups, which led to group-specific differences in prescribing recommendations.

This lack of racial/ethnic diversity in clinical trials unfortunately continues to hinder precision medicine and leads to "insufficient information pertaining to medical product safety and effectiveness for product labeling."[8] To counteract this, the US FDA recommends in their recent guidelines (Enhancing the Diversity of Clinical Trial Populations) the "[i]nclusion of racial and ethnic minorities in clinical trials and the analysis of clinical trial data by race and ethnicity [since

differences] in response to medical products (e.g., pharmacokinetics, efficacy, or safety) have been observed in racially and ethnically distinct subgroups of the U.S. population."[8] However, as race and ethnicity are primarily social constructs, words "used to define and describe race and ethnicity have changed with time based on shifts in sociocultural factors"[57] and may also be inaccurate. For example, the definition of "White" by the US Census Bureau is "A person having origins in any of the original peoples of Europe, the Middle East, or North Africa." This broad categorization discounts sociocultural factors that may affect someone's access to medical care and other barriers they may face (e.g., a person from the Middle East has very different experiences compared to someone of European descent). Even with the inclusion of diverse patients, inconsistencies in racial/ethnic definitions – particularly for clinical trials held across, and medications approved in, several countries – remains problematic with no easy solution. [58]

The underrepresentation of other populations in genomic databases[59] has also received special attention in recent years due to advances in technology and growing clinical datasets – particularly in the field of cancer genomics. For example, only 10% of specimens in research network biorepositories in the US are from non-white patients.[60] This underrepresentation is problematic as it limits the generalizability of genomic studies or biomarker tests, thereby limiting evidence-based targeted treatments of many cancers and genetic diseases that are rare in white or European populations.[59–61] Furthermore, differences in knowledge, attitudes, and experiences exist across racial/ethnic groups. For example, regarding whether to donate specimens for biobanking: African Americans referenced medical mistrust; Hispanic/Latino participants cited a lack of benefits; Vietnamese participants were apprehensive of physical aspects of donation; Hmong and Chinese participants wanted to know the use of biospecimens in research; and white participants were suspicious of exploitation by corporations.[62] Barriers regarding language only further decreased understanding and knowledge regarding biospecimens and their intent – highlighting the necessity of taking targeted approaches when addressing the concerns of specific groups.[62] By increasing the participation of racial/ethnic minorities, clinical trials play a crucial role in the improvement of health equity. Race and ethnicity are complex dimensions that need to be incorporated into clinical trial designs – however, whether racial/ethnic differences in responses to certain treatments are attributed to genetic differences between groups or are a surrogate for other socioeconomic differences and structural access-related barriers (e.g., access to healthcare, health literacy, education) is sometimes unclear.[42,51]

Often, barriers to participation stems from a lack of knowledge regarding clinical trials (or biobanks), having low health literacy, living in areas with poor access to healthcare or clinical

trials, language barriers, worries about data privacy, as well as historically grounded medical distrust and facing forms of discrimination (e.g., doctors are less likely to talk to ethnic/racial minority patients about clinical trials).[18,42,62] Some measures to address these include increasing cultural competency of site staff (e.g., diversity trainings), using decentralized methods (e.g., mobile vans, flexible study visit times, remote methods), increasing health literacy and communication (e.g., providing accessible materials), assuring safety and transparency, hiring more diverse staff, and using diverse images and local languages.[6,54,55,60,62–65]

3.2. Sex and gender

Prior to the NIH's Health Revitalization Act of 1993[10] which established guidelines for increasing the inclusion of women and minorities in clinical trials, women were largely excluded from clinical trials based on a 1977 guidance from the US FDA as a way to "protect the woman and any developing fetuses from harm."[66] However, due to biological differences between men and women that can lead to very different treatment responses, researchers and women organizations have called for the equal inclusion of women in clinical trials, as well as the analysis of sex-specific outcomes.[7,67] This push led to, for example, the development of the Women's Health Initiative[38] (see **Box 1**) and the Women's Ischemia Syndrome Evaluations study,[68] with both studies leading to changes in the assessment, treatment, and prevention of cardiovascular disease in women.[40,41,69] The need to include women in clinical trials is further highlighted by the statistic that showed women in the US suffered >2 million drug-related adverse events compared to 1.3 million in men between 2004-2013.[7]

Still, many studies that include women do not report or analyze data based on sex, with more women enrolled in Phase III clinical trials, and less in Phase I and II (phases that identify the safe and effective doses) clinical trials that typically enroll more men.[7] Furthermore, preclinical testing in animals are also biased towards males based on the pretense that male animals have less variation in their hormonal cycles – which was later proven untrue, with male mice showing as much or even more variation than female mice.[7,70] Kathryn Sandberg, a researcher at Georgetown University (Washington, DC) studying hypertension, remarked "You're biasing the whole drug pipelines towards what is optimal in the male."[7] This can lead to a potentially dangerous and delayed observation on efficacy and safety of medicines at a later stage of the drug pipeline – either at Phase III or on the market – wasting time and money and putting women at risk.[7]

"You're biasing the whole drug pipelines towards what is optimal in the male." – Kathryn Sandberg, researcher at Georgetown University (Washington, DC) studying hypertension[7]

However, recently in 2016, both the NIH and the European Association of Science Editors issued new stances[7,11]: the NIH stated that grant proposals with vertebrates must include both sexes and to analyze by sex (or have a reason not to); while the European Association of Science Editors created a Sex and Gender Equity in Research Guidelines asking journal editors to ask for results based on sex and gender. Still, despite these new guidelines, no distinction is made between sex assigned at birth (biological construct) versus gender (social construct), with some researchers suggesting the inclusion of both. Mapes *et al.* (2020)[54] state that "gender identity as a social determinant of health is not only understudied, but also under recognized…[with a] lack of knowledge and sensitivity of medical personnel about different gender identities" that can create further barriers with individuals who identify as gender-diverse. With growing awareness during the past decade, there has been more focus on barriers (and how to remove barriers) that Transgender and Gender-Diverse (TGD) patients face in clinical trial participation – although data is still extremely limited.[54,71]

Data on sexual orientation are also lacking – unless related to studies on STIs.[54,72] Within the LGBTQIA+ community, there is a strong distrust of medical institutions (rooted in mistreatment and discrimination as seen, for example, during the early years of the HIV/AIDs epidemic in the 1980s and 90s), despite interest to be involved in clinical research. While many of the barriers and concerns regarding participation may be similar to those faced by cisgender/heterosexual people (e.g., socioeconomic or financial barriers) and other minority communities (e.g., discrimination, lack of cultural understanding), there are also barriers specifically related to their gender identity/sexual orientation. For example, a review in the *New England Journal of Medicine* on 243 clinical studies of sexual function after medical treatment found that 37 studies specifically excluded people in a same-sex relationship.[73] Furthermore, barriers to clinical trial participation relating to sexual identity and sexual orientation are often intersectional, with those who identify as racial/ethnic minorities often facing additional barriers (such as through systemic racism and discrimination) compared to their white counterparts.[50,51,61]

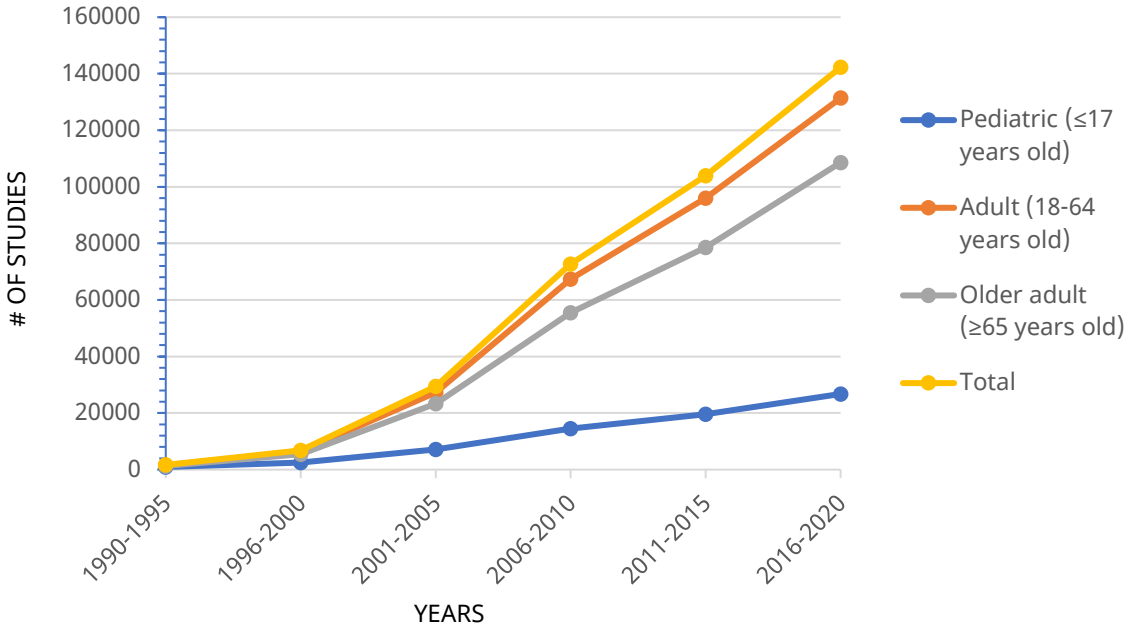
Some solutions to addressing barriers to minority participation of women, TGD, and LGBQTIA+ individuals includes taking a targeted approach as different groups have different needs in

communication and in the ways they receive healthcare information.[74] Addressing issues – such as discrimination, lack of cultural understanding by healthcare professionals, and fear of confidentiality – would most likely lead to more TGD and LGBTQIA+ individuals to participate.[75] Sponsors and other clinical trial stakeholders should work with women's and LGBTQIA+ organizations to disseminate information, hold culture and sensitivity training among investigators and site staff, and report sex at birth (including intersex), gender identity, and sexual orientation in studies.

3.3. Age

As you age, your body goes through physiological changes – affecting how medicines are absorbed by your body, which medicines you can take, and their dosage. Clinical trial populations are heavily biased towards young and middle aged adults (18–65 years old) (**Figure 3**),[54] with strict inclusion/exclusion (I/E) criteria or safety concerns that may prevent pediatric and geriatric patients from participating. For example, despite a growing aging population,[76] 30% of patients participating in clinical trials were 65+ years old[3]; and although 27% of the global population are children, only 16.7% of clinical trials are pediatric trials.[77] While some concerns may be warranted, such as higher comorbid conditions[78] in adults or fears over finding safe doses in children,[77] limiting their participation in trials only delays finding safe and effective medicines in these patient groups.

Figure 3. Number of clinical studies recruiting patients by age.



Number of clinical studies recruiting pediatric (≤17 years old), adult (18–65 years old), and older adult (>65 years old) patients over time on clinicaltrial.gov.

Older individuals, in particular, are disproportionately affected by various diseases and are more likely to receive medications or therapies,[79] but are still highly underrepresented in clinical trials as they typically do not meet the eligibility criteria in clinical trials or may even be explicitly excluded by some studies.[54] For example, although atopic dermatitis typically presents with higher prevalence among pediatric/adolescent populations, recent studies suggest a second peak in incidence after 60 years of age.[80] This again highlights the need to include older adults in clinical trials (and atopic dermatitis clinical trials specifically).

However, a systematic review of inclusion or exclusion criteria in trials of systemic atopic dermatitis medications found that 34% of trials explicitly excluded older adults (≥65 years old), 69% had other exclusion criteria that might disproportionately exclude older adults, and <5% of participants who received dupilumab (the first biologic approved to treat moderate-to-severe atopic dermatitis in 2017) for atopic dermatitis in clinical trials were ≥65 years old.[80] A search on clinicaltrials.gov also show that although a large proportion of clinical trials do not explicitly

exclude older adults (**Figure 3**), their overall actual participation still remains low (30% of clinical trials, 2020 U.S. FDA Drug Trials Snapshots Summary Report[3]). Several reasons exist, such as older adults may have more restrictions regarding comorbid conditions, concurrent medications, or perceived higher burden by site staff (e.g., longer screening periods, more retention tactics and support due to cognitive/physical impairments or disabilities).[54]

That elderly individuals are still underrepresented in clinical trials is also in contrast to the widespread adaption of the 1993 ICH-E7 guideline from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) that stated that medications should be studied across all ages, including older patients – and that patients in clinical trials should be "reasonably representative of the population that will be later treated by the drug."[79] Furthermore, researchers argue that merely including older adults in clinical trials does not make sense if the protocol design and study outcome analyses are not modified; as van Marum (2020)[79] points out:

> *"Inclusion of the elderly may also require different outcomes. In a geriatric population scales measuring feelings of autonomy, levels of psychological, social, and physical functioning may be more relevant than using outcomes such as survival or time to event."* – *Rob J. van Marum (Principal Investigator and Endowed Professor of Elderly Care Medicine at Amsterdam UMC)*

Clinical research should also include pediatric patients (<18 years old) as, explained by the World Health Organization (WHO), "Children are not just small adults – their bodies work in very different ways and they often undergo many changes as they grow from infancy towards adolescence and adulthood." Therefore, the most effective way to find new treatments for children is to find safe ways to enroll them in clinical trials. Given this vulnerable population, pediatric patients require additional considerations when designing clinical trials and creating children-specific protocols.[81,82] Currently, the FDA only approves certain medications in different pediatric groups after initial approval in adults. For example, dupilumab was first approved in adults, then in children ages 12-17 years old, followed by ages 6-11 years old, and is under investigation in children 6 months to 5 years old – despite approximately 90% of patients experiencing onset of atopic dermatitis before 5 years of age.[83]

The lack of pediatric trials has led to situations where pediatric patients are treated with medicines off-label – creating a "knowledge gap regarding efficacy and safety of medicines in children."[84] Hoon *et al.* (2019)[85] found that between 2006–2015, treating physicians of pediatric patients were increasingly prescribing off-label medications during 18.5% of visits – with as many as 83% of visits including neonates. However, despite recent legislation in North America[86,87] and in the European Union[86,88] on recruiting patients for pediatric trials, challenges still remain due to difficulties surrounding consent/assent to procedures, low health literacy, need for age-appropriate information, safety concerns from caregivers/parents/guardians, as well as study design issues including children-specific protocols, smaller sample sizes, and strict I/E requirements.[77,81,84,89]

Critics have argued that the underrepresentation of these groups only continues to limit the conclusions that can be drawn from clinical trials about the generalizability, efficacy, and safety of treatments for both children, adolescents, and older adults. Clinical trials need to consider age-related prevalence when recruiting specific patient populations, particularly as certain conditions and diseases exhibit marked age-related differences in prevalence (e.g., Alzheimer's in older patients, atopic dermatitis in young children). Some solutions to help increase clinical trial participation include changes in study design to accommodate adults and children (e.g., less study visits, remote monitoring, flexible hours), more support regarding knowledge and awareness (e.g., age-appropriate and accessible information across the full age spectrum), using digital outreach to reach family members and caregivers during recruitment, higher retention tactics (e.g., visit reminder cards, regular contact), reassuring safety and informing the benefits of trial participation (e.g., providing study materials), community-based partnerships, as well as addressing ageism and building trust with medical and clinical staff.

3.4. Location

Patients who live in rural or non-metropolitan areas, as well as those in non-Western countries, tend to face higher barriers when it comes to clinical trial participation[54] – such as a lack of transportation, distance to sites, less access to healthcare, lower health literacy, and less general awareness regarding clinical studies.[54,60,90] Furthermore, location falls within an intersectional framework as it is highly tied to socioeconomic status and education (with lower income and less than a high school education or equivalent also leading to less participation).[54] To further complicate matters, large geographic differences in the prevalence and incidence of different

diseases and conditions also exist due to a combination of local environmental risk factors, socioeconomic status, access to and quality of healthcare, as well as other population demographic and non-demographic factors.[91–93] This is particularly concerning as rural areas often have worse health outcomes due to less access to healthcare, lower income, and less education. Additionally, race/ethnicity are also strongly linked to location in the US (e.g., International Districts, Indigenous Reservations), with the US' Zip Code Analysis Project showing that 80% of Americans who identify as minorities live in 20% of US Zip codes.[94] Racial/ethnic minorities also typically have different doctors and attend different hospitals and clinics compared to non-Hispanic white patients – even when living in the same neighborhoods.[95] Patients may also show a preference to see primary care doctors of the same race/ethnicity – although minority doctors may also tend to practice in closer proximity to minority communities.[95]

Some measures and interventions to improve the inclusion of patients across larger geographic ranges, as well as undeserved rural populations, include community outreach programs, building relationships with community health workers, improving clinical trial awareness through accessible health literature, digital outreach focusing on specific areas, using decentralized methods (e.g., mobile vans), communicating in local languages, and cultural competency training. In some countries without universal healthcare, having clinical sites in local community clinics and hospitals for people who are less likely to have health insurance coverage can also allow for more diverse populations to participate.

3.5. Other determinants

Other determinants that are less often, or not reported at all, can also affect someone's ability to participate, such as education, access to healthcare, and household income, as well as comorbid conditions, visible and non-visible disabilities, and cognitive/mental impairments. [61,96–98] In particular, education (highly linked to socioeconomic status) proves to be an important factor in clinical trial participation. Overall, studies from both the US and Europe show that people with a degree from college or university are more likely to participate – with these results also mirrored in racial/ethnic minorities with higher education.[54,60,65,99] Indeed, Meyer *et al.*(2021)[99] found that racial/ethnic minorities, those with a median income >$50,000, and middle-aged adults were more likely to participate in oncology trials.

Also patients with comorbid conditions, disabilities, and cognitive or mental impairments face more difficulties in trial participation due to issues surrounding consent/assent and the need for more support (e.g., transportation, guides, sign language interpreter) depending on their condition.[54,100,101] In clinical trials, patients with comorbidities are often excluded due to strict I/E criteria to rule out the possibility of complications from their condition or concurrent medications they may be taking.[97] For example, patients with diabetes, hypertension, and kidney disease in particular are often excluded, which indirectly leads to the exclusion of people from different racial/ethnic backgrounds and of lower socioeconomic status, where these conditions and diseases are more common. For this reason, researchers are increasingly pushing for the re-evaluation of I/E criteria for patients with comorbidities.[102]

Additionally, according to the WHO,[103] 15% of the global population currently experiences a disability – with this number continuing to grow due to an ageing population and increase in noncommunicable diseases.[104] Individuals with disabilities also tend to have worse health outcomes and are less likely to receive proper healthcare services and care, while facing daily discrimination.[96,101,103] Lack of inclusion of patients with certain disabilities or impairments prevents these patients from receiving safe and effective therapies and only further creates growing divide in health equity.[96,101,103,105] Furthermore, clinical scientists are increasingly arguing that there are also “scientific” or methodological reasons and ways of including people with

disabilities.[106,107] To ensure greater healthcare access to patients who face additional barriers, those involved in clinical trials need to address transportation issues (e.g., mobile vans, less study visits), provide financial compensation, include lay-friendly study materials, increase health literacy, provide sign language interpreters (and other guides/assistance), have flexible study visits (as lower-income people have less job flexibility), and perform community outreach efforts.

3.6. Outlook

Besides a better understanding of different patients and the communities they come from, being able to accurately target, recruit, and retain patients continues be a challenge for many clinical trials. Being unable to enroll enough patients remains one of the major reasons for trial terminations, with the Clinical Trials Database reporting that 55% of trials were terminated due to low enrollment.[108] Furthermore, >80% of trials fail to enroll enough patients on time – leading to study extensions and mounting costs.[108] Throughout the trial life cycle, clinical trials also face issues with patient adherence to treatments and retention, with some studies citing dropout rates of 20% or more – reducing statistical power to determine efficacy of treatments and resulting in possible biased trial conclusions.[109,110] Additionally, recruiting patients often means discussing options and sharing responsibility with the patient's support network.[111] Therefore, providing better support to both caregivers and patients throughout the trial are needed to improve recruitment and retention in clinical trials.[60,63,111]

Despite growing interest in DEI in clinical trials (**Figure 1**), the underrepresentation of certain underserved or minority populations still prevents us from accomplishing precision medicine and increasing social and health equity. Furthermore, the lack of consistent data collection and reporting on certain dimensions of diversity leads to gaps in knowledge that prevents us from specifically addressing certain barriers and leads to further health disparities. Besides lower enrollment in clinical trials, racial/ethnic/sex/gender minorities, older patients, patients who face language barriers, patients with disabilities, and patients in rural areas are also more likely to drop out and be Lost-to-Follow-up.[112–114] Only by taking a intersectional and multi-level approach towards understanding who patients are and the specific barriers they fac can we finally begin to improve health access and care for everyone.

Interested to learn more about what Clariness does to improve DEI in clinical trials?

Contact us here to learn more.

4. What are solutions to improving DEI in clinical trials?

Researchers have highlighted several ways to improve DEI in clinical trials. Some of these are general measures that various stakeholders can take to make their study populations more inclusive; others are group-specific measures that target specific barriers that certain individuals or communities may face (keeping in mind that several identities may reside in one individual).

Figure 4. Improving DEI in clinical trials.

Solutions to increasing diversity, equity, and inclusion in clinical trials.

4.1 Summary of group-specific measures to improve DEI

While some generic measures can be taken to make clinical trials more inclusive, clinical trial organizers can also take group-specific measures to facilitate DEI (**Table 1**) – with certain measures that may overlap between groups. Although we have divided the **Table 1** based on certain dimensions of diversity, please keep in mind that improving DEI requires applying an intersectional framework as individuals are multidimensional and do not fall within one category.

Table 1. Examples of group-specific measures to facilitate DEI in clinical trials.

Race and ethnicity		
Redesigning studies	**Recruitment and increasing clinical trial awareness**	**Increasing health literacy and communication**
1. Including input from minority communities in study design 2. Providing compensation 3. Selecting study sites in or near minority communities 4. Using decentralized methods (e.g., remote monitoring, mobile health vans, less study visits, etc.) 5. Report race/ethnicity data (and research appropriate definitions)	1. Digital outreach campaigns using diverse images and local languages 2. Hosting community events and performing community outreach (particularly among community clinics, local pharmacies, or churches) 3. Providing accessible study materials in local languages using diverse images	1. Providing content explaining the study and clinical trials in general 2. Providing general health, medical, and treatment information 3. Training clinical and medical staff on how to explain complex concepts to patients 4. Cultural and diversity competency training for clinical trial stakeholders (e.g., site staff, study doctors) 5. Communicating transparency and addressing concerns over safety and privacy

Sex and gender		
Redesigning studies	**Increasing trust**	**Increasing health literacy**
1. Involving LGBTQIA+ patients and advocacy groups in study design 2. Providing compensation 3. Reporting on both sex at birth and gender	1. Digital recruitment efforts that include gender and sexuality sensitive content 2. Sensitivity training for all medical and clinical staff 3. Assigning a trusted or confidential contact person that can address specific concerns related to gender and sexuality 4. Communicating transparency and addressing concerns over safety and privacy	1. Information explaining the need for diverse participants in clinical trials 2. Involving women and LGBTQIA+ platforms and community places to help spread information 3. Providing additional health, medical, and study materials

Age (pediatric and older adults)		
Redesigning studies	**Increasing trust**	**Recruitment and increasing health literacy**
1. Using decentralized methods (e.g., remote monitoring, mobile health vans, less study visits, etc.) 2. Facilitating transportation or caregiver assistance 3. Flexible schedules for parents/caregivers 4. Providing compensation 5. Including patient appreciation gifts 6. Reviewing I/E criteria	1. Informing patients and caregivers regarding the importance of clinical research 2. Community-based partnerships with homecare centers and elderly homes and institutes 3. Addressing awareness, distrust, and ageism 4. Communicating safety and addressing concerns over safety and privacy	1. Digital outreach to family members and caregivers 2. Accessible and age-appropriate study materials for pediatric patients, older adults, and caregivers/parents 3. Providing informed consent aids 4. Training clinical and medical staff on how to explain complex concepts to patients

Location		
Redesigning studies	**Recruitment and increasing clinical trial awareness**	**Increasing health literacy and communication**
1. Using decentralized methods (e.g., remote monitoring, mobile health vans, using local community clinics, etc.) 2. Providing compensation 3. Providing travel to sites and overnight stays	1. Hosting community events and performing community outreach (particularly among community clinics, local pharmacies, or churches) 2. Providing study materials in local languages using diverse images 3. Mobilizing community coalitions that include local representatives	1. Digital outreach focused on specific areas 2. Providing study materials in local and regional languages 3. Cultural competency training for staff

Other determinants		
Redesigning studies	**Recruitment and increasing clinical trial awareness**	**Increasing health literacy and communication**
1. Using decentralized methods 2. Providing compensation 3. Reviewing I/E criteria 4. Reporting on other diversity metrics 5. Providing transportation or caregiver assistance	1. Sensitivity training for all medical and clinical staff 2. Informing patients and caregivers regarding the importance of clinical research	1. Providing accessible study materials 2. Including informed consent aids 3. Training clinical and medical staff on how to explain complex concepts to patients

4.2 Examples of strategies to improve communication with patients

Beyond regulatory changes and redesigning studies, many barriers stem from a lack of communication and understanding.[6,54,60,63,65] In fact, many patients from underrepresented and/or minority communities show just as high willingness to participate as white patients – they simply aren't asked to or are not made aware of clinical trials.[47,54,60,65] Still, other barriers, such as racism and discrimination, or concerns over medical safety and health need to be addressed. Below, we've compiled examples on how to communicate with patients based on specific barriers adapted from Clark *et al.* (2019)[63] and Garcia *et al.* (2022).[42]

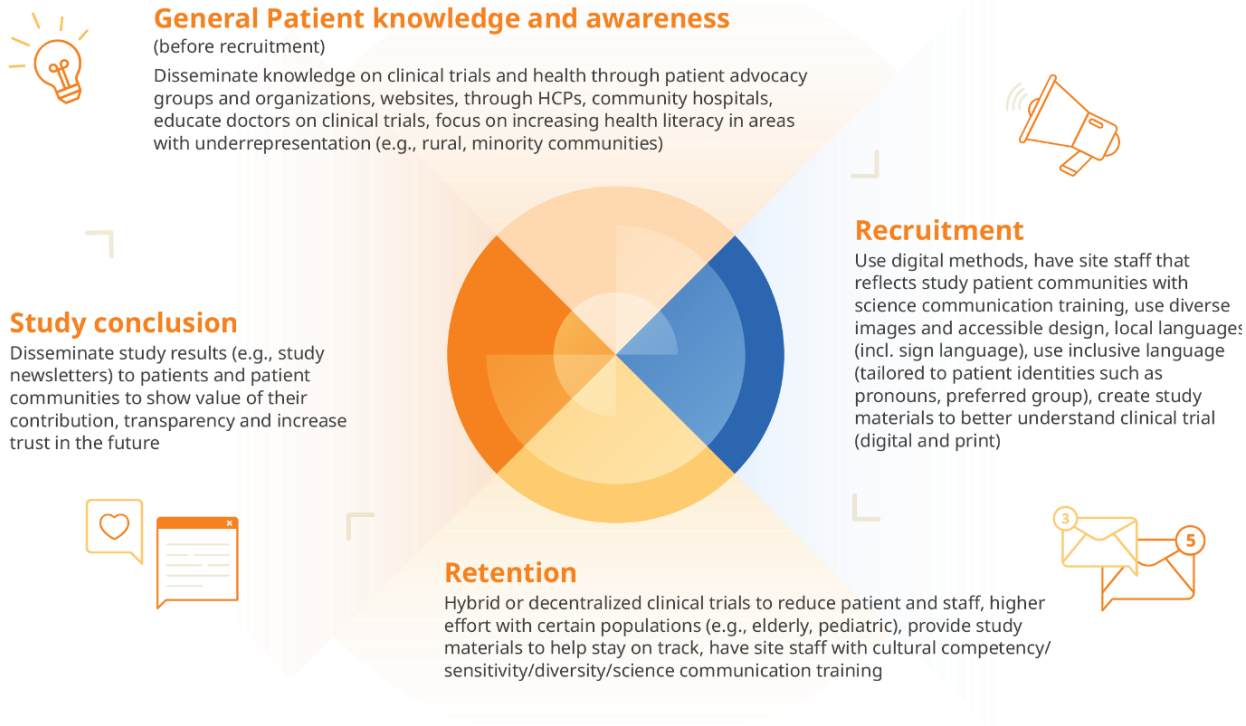
Table 2. Overcoming barriers and communicating with patients adapted from Clark *et al.* (2019)[63] and Garcia *et al.* (2022). [42]

Barriers	Solutions	Examples of communication
Medical mistrust		
• Historical basis • Fear • Racial/ethnic/sex/gender discrimination • Cultural insensitivity • Poor/lack of communication from HCPs • Social stigma	• Reinforce patient's personal safety/health • Use culturally appropriate language • Transparency • Assure participation is entirely voluntary • Show appreciation • Involve the patient's support network in decision-making • Explain the value of their contribution	• "Your health and safety are important to us" • "Your participation is entirely voluntary – you can stop at any time" • "We will closely monitor your health and any side effects you may have" • "All types of people are needed to join studies, so we know how treatments works in different people of all ages, races/ethnicities, and genders"
Communication		
• Low health literacy • Poor HCP-patient relationship • Lack of trust • Fear over safety • Lack of understanding regarding the study and their responsibilities	• Use plain, simple language • Give patients opportunities to ask questions and give complete/ transparent answers • Take time to talk and provide materials to take home • Reassure patient experiences and fears	• "We want you to have all the information you need to make a good decision about being in the study" • "We appreciate your interest – participating in this study will benefit others with your condition in the future" • "We are here to provide support and answer all your questions"

Barriers	Solutions	Examples of communication
Culture and language		
• Racial/ethnic discrimination • Cultural insensitivity • Materials not in patient's language • Site staff does not speak patient's language	• Understand where the patient is coming from • Try to understand cultural barriers and taboos • Communicate in the patient's language (including sign language or braille) • Use diverse and inclusive language and images • Involve the patient's support network in decision-making • Show appreciation	• "We will watch how well you are doing throughout the study and share information with you" • "We are here to answer questions and listen to your concerns" • "Please let us know if you understand and what we can clarify for you" • "Do you need an interpreter?" • "Please let us know if you feel uncomfortable or do not understand something"
Financial and time constraints		
• Financial burden and compensation unclear • Loss of working hours • Travel and overnight stays • Family obligations	• Clearly explain the patient's responsibilities throughout the study • Be transparent about costs and time involved • Provide compensation • Be flexible to accommodate patients (e.g., limit number of study visits, remote monitoring, etc.)	• "You will know what to expect at all times so that you feel in control" • "Please let us know if your responsibilities are unclear and how we can accommodate your needs" • "Please let us know if you are unable to attend study visits so we can come up with a solution"

Furthermore, improving patient recruitment and retention, as well as general clinical trial awareness, requires multilevel strategies with the right messages and strategies presented at the right time.[63] Therefore, we recommend building awareness and supporting patients in appropriate ways that are adapted across the clinical trial life cycle (**Figure 5).**

Figure 5. Patient-centric strategies to improve patient knowledge, recruitment, and retention in general and among underrepresented/minority groups.



5. How does Clariness fit in?

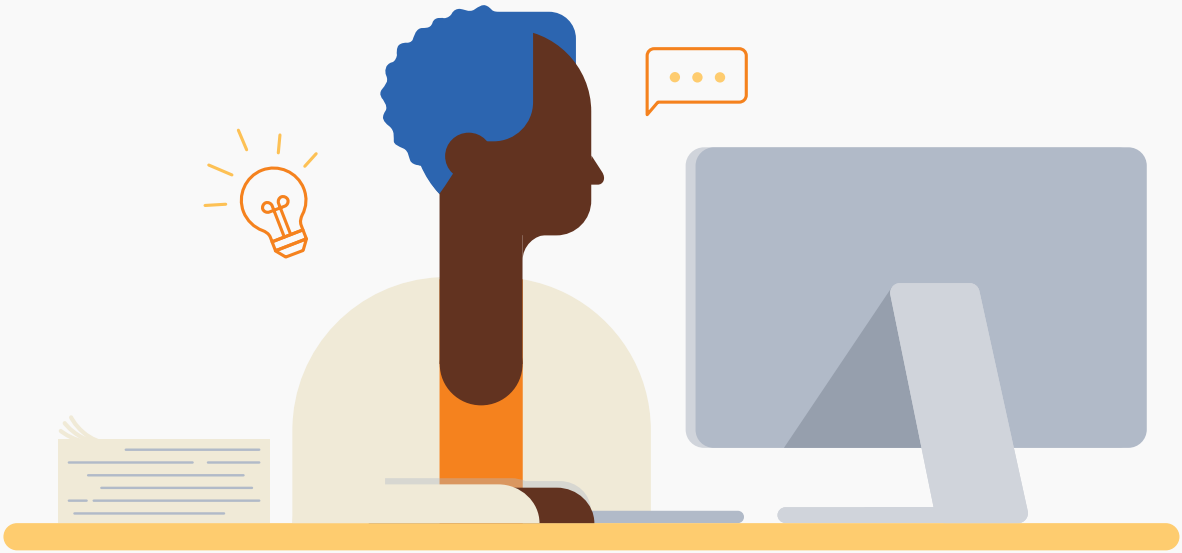
At Clariness, our Mission is “to improve patients’ lives by accelerating the development of new medical therapies.” To do this, we take a multilevel approach connecting patients, sponsors, and sites on our ClinLife patient portal. As a diverse company, with people all over the world from various backgrounds and speaking over 35 languages, we are committed to overcoming barriers to diversity in clinical trials and are motivated to help organizers improve DEI in their study populations and patient engagement materials.

We believe that our data-driven and patient-centric approaches to patient recruitment can accelerate the way towards more inclusive and representative clinical trials. Our services are tailored to facilitating and improving the complete patient journey in clinical trials in 4 steps.

5.1. Our steps towards improving DEI

Step 1: Listening to and understanding patients

We believe that to improve diversity requires an understanding of the patient – and to achieve understanding requires active listening. We regularly implement our patient surveys (through Patient Insights and Clinlytics teams) to ask patients about their needs, wishes, attitudes, and opinions about clinical research. Next, our medical teams perform a deep dive into the scientific literature, as well as read patient testimonials and experiences to better understand their pain points and barriers faced by patients. By performing demographic analyses around clinical study sites, we gather insights on patient communities and their distance to sites. This allows us to address one of the largest barriers to patient participation by making recommendations on site selection, as many study sites are traditionally located closer to affluent and/or non-Hispanic white communities. Gaining an understanding of the various (intersectional) barriers patients may face informs our subsequent outreach campaign and can also be used to make recommendations to our partners regarding trial locations or protocol designs based on patient needs and location.



Want to know how we can make your clinical trials more patient-centric? Reach out to us here.

Step 2: Improving health literacy and communication

One way to overcome key barriers to DEI in clinical trials is to improve health literacy and communication. In 2021, we launched our new patient blog (currently available in Germany and coming soon to Poland) where we provide easy-to-understand information about clinical research and procedures, as well as safety and ethical checks to address general and group-specific concerns. Furthermore, our Creatives Team ensures that each study and recruitment materials are accessible (language, wording, and design), uses diverse images, and are translated into local languages.

As 9 out of the 10 most-spoken languages have gendered terms,[115] we also work with language specialists to try and use inclusive language – particularly regarding gender-neutral and gender-inclusive languages (e.g., use of pronouns). While only a first step that still requires further actions, representation matters and is an important move towards ensuring patients feel heard and seen.

We also use social media to engage with patients by answering questions or providing information regarding health and clinical trials. More recently, we've partnered with sponsors to create websites for specific studies with study-related and health-related information. To improve patient retention, we offer intensified support communicating regularly with patients to help them schedule visits and set up reminders – all in their local language. This helps to keep patients engaged and troubleshoot any issues quickly.

Step 3: Erasing geographical barriers when reaching out to patients

The global number of social media users has risen by almost 10%[116] in the last 12 months to 4.55 billion users, equating to around 1 million new users every day. This statistic becomes even more relevant when combined with the fact that the internet is increasingly used as an important source of health information, with over 72% of people using "Dr. Google" to inform themselves

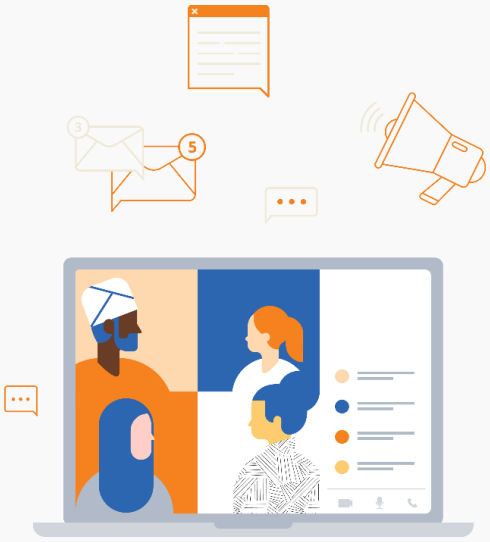
on health-related topics.[117] Understanding this, we implemented a recent successful recruitment campaign for a dementia study showing that the right digital patient recruitment strategy can reach and enroll elderly patients (an often difficult to reach patient group) with dementia. We used a strategy that focused on both patients and their caregivers, as well as different online groups for dementia. This study was entirely decentralized and based on telephone and home visits, leading to reduced patient burden and fewer drop-outs.

In another study recruiting patients with systemic lupus erythematosus, we were asked to specifically recruit Black/African American patients given a higher prevalence of lupus in these patients. By targeting our digital outreach to Black/African American communities, we were able to recruit these patients at the same costs as non-Hispanic white patients. This experience supports evidence from other trials that shows these communities are either less aware of or not asked directly to participate in clinical trials. However, even if you target certain underrepresented communities, site selection is often the next barrier to participation. Additionally, less diverse study teams (with no diversity or sensitivity training) combined with language barriers are further barriers and highlights the need to apply DEI across all aspects of running a clinical trial.

Besides searching for health-related information, being online allows patients to find support groups, as well as vocalize issues surrounding inequality and discrimination by placing it directly on the public agenda – and we firmly believe in being a part of this conversation. By being able to base outreach efforts on characteristics such as age, interests, search activity, and location, as well as education level or employment, we believe digital recruitment is able to reach people who

are undiagnosed, fall outside of the healthcare system (or even society), or lack general clinical trial awareness and give them access to healthcare. Based on data from our Patient Insights and Clinlytics team, as well as our 16+ years of experience, we are able to continually evolve and coordinate our digital outreach efforts to help ensure that underrepresented and minority patients feel represented in clinical trials.

Step 4: Hosting the Annual's Patient's Voice



We want patients to feel heard. Our annual Patient's Voice Conference helps connect patients to sponsors and others at the forefront of the clinical industry. Every year, we invite patients to share their experiences and challenges they face. This allows sponsors, sites, and medical experts to gain a deeper appreciation of the what patients go through when accessing clinical trials and throughout their participation. We hope this conference opens up a dialogue that can spark change within the industry to become more patient-centric and leads to improvements in clinical trial processes and designs.

6. Summary: Our key takeaways

By increasing the participation of underrepresented and minority patients, clinical trials can begin to improve social and health equity through targeted precision medicine. Diversity is complex and multidimensional – requiring a multilevel and intersectional approach to be successfully incorporated into clinical trial designs. However, whether certain patients respond differently to certain treatments are due to (epi)genetic differences between groups, or are a surrogate for other social/environmental/socioeconomic differences or structural access-related barriers (e.g., access to healthcare, health literacy, education) is often unclear. But to even begin to disentangle these effects – we first need to include more diverse patients, as well as analyze and report the data to understand how different patients are affected by different medicines.

Often barriers to minority participation stems from a lack of knowledge regarding clinical trials (or biobanks), having low health literacy, living in areas with poor access to healthcare or clinical trials, language barriers, worries about data privacy, as well as historically grounded medical

distrust, and facing forms of (systemic) racism or discrimination (e.g., doctors are less likely to talk to racial/ethnic minority patients about clinical trials). Some measures to address these include increasing cultural competency of site staff, using decentralized methods (e.g., mobile vans), increasing health literacy and communication (e.g., providing study materials), assuring safety and transparency (e.g., communication training), hiring more diverse staff, and using diverse images and local languages (including sign language and braille). With some barriers starting to become more clearly defined, now is the time for clinical trial stakeholders to act and remove them (**Table 3**).

Table 3. Our actions towards achieving DEI in clinical trials.

Patients
Understand patients • Perform patient surveys • Host Patient's Voice **Reach and recruit patients** • Perform digital outreach campaigns • ClinLife Newsletters **Enhance health literacy and communication** • Create accessible study materials, study websites, and general health content • Create patient blogs • Use gender-inclusive language, local languages, and diverse images to help patients feel seen and heard **Improve retention** • Help patients keep track of study visits (e.g., SMS, appointment reminder cards) • Support decentralized methods that reduce patient burden and keep them engaged
Sponsors
Understand patients • Perform patient surveys • Host Patient's Voice **Reach and recruit patients** • Patient recruitment and outreach • Assist in site selection (based on patient demographics and location) **Enhance health literacy and communication** • Work with sponsors to create accessible study materials (both patient- and site-facing), as well as study websites **Improve retention** • Navigate how to implement decentralized methods

Sites

Reach and recruit patients

- Our Enrollment Managers support sites and reduce burden
- Create study materials for sites to use to talk to patients to improve communication

Improve retention and communication

- Study website for HCPs
- Site newsletter

Patient organizations, advocacy groups, research institutes, and industry leaders

Understand patients

- Form collaborations (learn more about our partners here)

Reach and recruit patients:

- Engage with patient advocacy groups and organizations

Enhance health literacy and communication

- Collaborate on creating content for patients

Our Mission at Clariness is "to improve patients' lives by accelerating the development of new medical therapies." We can only achieve this through building long-term community engagement and active listening as clinical trials evolve to become more patient-centric. We are committed to increasing diversity, equity, and inclusion in clinical trials and believe that engaging with various clinical trial stakeholders can foster trust and communication to create new strategies and solutions that tackle barriers to DEI and activate change. We intend to play a pivotal role in improving health equity by creating partnerships and through action – will you work with us to achieve this mission?

If you have any questions on how to improve DEI in your clinical trials – or if you are a patient advocacy group, patient organization, or industry leader who would like to partner with us – please contact us. You can also learn more about our patient-centric methods to DEI on our Patient Diversity page.

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