Diversity, Equity, and Inclusion in Clinical Research: A Path Toward Precision Health for Everyone

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Healthcare disparities are a persistent societal problem. One of the contributing factors to this status quo is the lack of diversity and representativeness of research efforts, which result in nongeneralizable evidence that, in turn, provides suboptimal means to enable the best possible outcomes at the individual level. There are several strategies that research teams can adopt to improve the diversity, equity, and inclusion (DEI) of their efforts; these strategies span the totality of the research path, from initial design to the shepherding of clinical data through a potential regulatory process. These strategies include more intentionality and DEI-based goal-setting, more diverse research and leadership teams, better community engagement to set study goals and approaches, better tailored outreach interventions, decentralization of study procedures and incorporation of innovative technology for more flexible data collection, and self-surveillance to identify and prevent biases. Within their remit of overlooking research efforts, regulatory authorities, as stakeholders, also have the potential for a positive effect on the DEI of emerging clinical evidence. All these are implementable tools and mechanisms that can make study participation more approachable to diverse communities, and ultimately generate evidence that is more generalizable and a conduit for better outcomes. The research community has an imperative to make DEI principles key foundational aspects in study conduct in order to pursue better personalized medicine for diverse patient populations.

Disparities in healthcare delivery and subsequent outcomes continue to be a persistent and tragic challenge in our society. Many contributing factors can be traced to structural forces at play in our society at large. While race, gender, or age are overarching disparity drivers, it is worth considering whether socioeconomic or educational attainment disadvantages (which affect some demographic groups disproportionately) are also causing significant gaps in our current complex healthcare ecosystems.

Healthcare stakeholders have a unique vantage point and opportunity to reflect on specific issues rooted in our environment and to propose solutions. Some issues affect healthcare delivery, such as systemic incentives to achieve efficiency or financial sustainability, or structural feeds of our workforce pipeline. This review focuses on the evidence generation efforts that support therapeutic improvements, and how they may be suboptimal for the effective deployment of those advances in diverse populations in need. Even as modern clinical research has brought improvements in medical care across multiple diseases, for minority groups, outcomes continue to lag in numerous health domains.[1]

In certain diseases, outcome disparities may be a composite result of genetic and environmental factors,[2,3] and research efforts lacking in diversity leave the medical community catching up to understand that interplay. In the United States specifically, some examples highlight how societal drivers appear to play a major role in health disparities. Diabetes, particularly type 2, is a disease where minorities bear a disproportionate risk and where longstanding determinants such as socioeconomic status (SES), residential segregation, educational attainment, or availability of adequate support for disease self-management conflate into dramatically unfavorable outcomes.[4–6] In that same health continuum, there are major outcome disparities in chronic kidney disease (CKD), which sit at the nexus of cardiovascular and kidney health.[7–10] Globally, heart failure provides another case in point where the misalignment between research thrust and disease burden is apparent. Low-income and middle-income countries where disease burden is highest are underrepresented in clinical trials for heart failure.[11] While in these and other areas there is room for improvement on how patients receive the care they need, it is also legitimate to interrogate whether research approaches, oftentimes single-mindedly focused on demonstrating efficacy in experimental settings, are optimized to generate insights about actual effectiveness in living environments.

Historically, clinical research efforts have been too narrowly designed to generate evidence valid and valuable across the reality of diverse patient populations. If we are to improve this situation, we have to understand the specific pitfalls that have fueled blind spots on traditionally conducted research. These blind spots span throughout the translational pathway from research to care, leaving entire communities underserved, and feeding a vicious cycle of widening disparities. We could map the eventual solutions to overcome those pitfalls and achieve outcome equity along that same pathway: When the direction is set for preclinical or technological discovery approaches, do they acknowledge genotypic/phenotypic diversity or all relevant societal determinants? When

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Received September 15, 2022; accepted November 18, 2022. doi:10.1002/cpt.2804

clinical research and clinical development programs are scoped, are they inclusive of all relevant communities, with appropriate engagement efforts? Do regulatory authorities set demands and expectations conducive to the generation of generalizable evidence, and are they engaging communities to better understand which evidence is needed? Are we researching the effects of the existing gaps in care access, or the impact that healthcare workers interacting with patients have? Do the benefits of cutting-edge evidence reach communities at the same pace or feed into existing gaps?

As we review these questions, several cross-cutting themes may be worth mentioning: as research programs do not start from blank slates, lack of representativeness in foundational data may be a shortcoming that seeds bias from the design of studies all the way to implementation of evidence; community engagement throughout the research pathway is an aspect often overlooked; moreover, there is room for improvement in the healthcare workforce (and, importantly, in its leadership roles) regarding diversity, cultural competence, and attention to health literacy issues.

The focus of this review will be on clinical research, which we define as activities including prospective clinical trials, observational studies, and real-world evidence. Improving the diversity, equity, and inclusion (DEI) of clinical research efforts is a key factor in the overall pursuit of health equity. We posit that evidence generation optimized to be representative of all communities enables the identification of the best possible intervention for each individual, eventually unlocking best possible outcomes at the population level.

WHY DEI IN CLINICAL RESEARCH?

The World Health Organization (WHO) defines health equity as the absence of unfair avoidable or remediable differences in health among population groups defined socially, economically, demographically, or geographically.[12] The path toward health equity is complex and encompasses a wide array of elements well beyond healthcare systems. However, there is ample evidence that, within their specific purview, health systems often fail to deliver on the basic tenets of equitable care.

As mentioned earlier, one such example can be found in the current landscape of CKD in United States. Deep disparities in care and outcomes persist by race/ethnicity and by SES, with Black and Hispanic patients with CKD, and those on the lowest strata of the neighborhood social deprivation index, experiencing worse outcomes.[1,13] While genetic differences across races could play a role in the etiology of the disease,[14] ancestry by itself does not seem to be the basis for differences in health outcomes related to kidney function.[8] Even the use of key diagnostic tools to guide interventions already shows knowledge gaps about the optimal approach to the incorporation of race, for instance in glomerular filtration rate calculations.[15] Multiple studies have identified differences in access to specific interventions, such as home dialysis or transplant for patients with end-stage CKD.[9,10,13] Those disparities reveal systemic care flaws feeding outcome differences. But we are lacking the deep understanding about the underlying contributing factors that would allow us to find solutions. In an example of the interplay of health care with larger social determinants, outcomes for Black men with advanced CKD receiving hemodialysis (therefore with basic access to the intervention) have been reported to be dependent on their place of residence, with certain communities showing increased risk for hospitalization and overall mortality.[9] This is an area with pressing unmet needs for a diverse population where minority groups bear a disproportionate burden. Yet, while an ideal estimate of representation in CKD clinical trials would suggest 35% as an enrollment target for Black or African American participants,[16] a survey of clinical studies reported in 2022 indicates most trials stand below that estimate, ranging between 5% and 29%,[17–24] and only one report showed 58.8% of African American participants.[25] This situation warrants a push for more inclusive research.

Disparities also play out at the international level. For instance, the burden of cardiovascular diseases falls disproportionately on low-income and middle-income countries, which are underrepresented in the clinical research ecosystem.[11] But recent research developments illustrate the value of more geographically inclusive efforts. Dietary salt intake is a highly regionalized aspect in the epidemiology of heart failure, particularly affecting low-income and disadvantaged populations. Studies investigating dietary replacement strategies have departed from the usual focus on US or EU countries, toward countries where this consideration is most relevant, such as rural China[26] and Peru.[27] These studies provide examples of some themes discussed later on in this review, such as locally grounded research leadership and recruitment efforts tailored to the realities of a specific environment. Furthermore, these studies fit the needs of these resource-constrained communities, where dietary interventions would be more feasible than pharmacologic ones, highlighting another valuable aspect of pursuing evidence that serves the communities for which it is intended.

Representativeness is therefore a key building block toward health equity and ultimately precision or personalized medicine, in other words, to produce the best possible outcomes for all individuals. Successful personalized medicine for all patients will depend on two pillars. First, the generation of robust generalizable evidence that can inform the best possible decisions for diverse populations. To accomplish this, clinical research initiatives have to be representative of the populations of interest. And second, the purposeful and effective incorporation of that evidence into practice, once it becomes available, must overcome barriers contributing to the lack of equity.

In clinical research, we understand DEI extensively, spanning multiple dimensions: gender, sex, sexual orientation, race/ethnicity, age, disability, nationality, SES, language, and political perspective. In the spectrum of clinical research, DEI should be incorporated in the development of therapies and diagnostics, as well as other medical technologies and algorithms. The design, testing, calibration, and deployment of any medical product should be based on research conducted in representative study samples, in order to generate evidence that can guide practice with greater confidence in predictable outcomes and safety profiles across different populations (i.e., to facilitate precision medicine for all).

STRATEGIES TO OPTIMIZE DEI IN CLINICAL RESEARCH

How do we generate optimal evidence to support healthcare practices relevant across communities? Novel clinical trial designs and emerging technologies give us multiple opportunities, as the

clinical development paradigm shifts toward earlier approvals and greater reliance on postapproval monitoring. We review below approaches to infuse DEI into the entire clinical research pathway (**Figure 1**).

Intentionality and goal-setting

This is the first consideration that can shape the overall direction of a study or research initiative. If the main intention of a study is to address representation gaps, its design should bring specificity in support of that intention; in turn, those specifications will allow tracking progress, and eventually holding accountability. For instance, the Research Goes Red initiative (sponsored by the American Heart Association and Verily)[28] was designed to address persistent gaps in understanding and managing cardiovascular disease in women. This registry is intended to reflect the demographic composition of the US population and to be open to study designs with specific end points of interest for the target population. For instance, the Research Goes Red Weight Study is investigating links between weight changes, physiological and behavioral factors (collecting biometrics, laboratory values and questionnaire based measures), and cardiovascular disease in women undergoing the menopausal transition. Another example within Research Goes Red, the Millennial Women's Heart Health Study will measure awareness and action regarding cardiovascular health using social media metrics, with the specific aim of understanding (and subsequently optimizing) the engagement of underrepresented millennial women from racial/ethnic minorities. The analytic pursuit of those end points informs recruitment goals within the underlying registry, which eventually dictate engagement efforts in the target population(s).

Diverse communities have to be effectively engaged in research initiatives

This has to be considered early on and in a sustained fashion. Research teams have to approach the communities that they are attempting to serve in order to understand their preferences and their needs. This engagement has to be bidirectional, with study teams "listening to" as much as "talking to" the community. Mechanisms that rely on community advisors can be particularly valuable,[29–31] as are approaches that find trusted community partners for their ground operations. The strategy of activating community members as "peers" to foster engagement in self-care has provided some initial success in lesbian, gay, bisexual, transgender, queer (LGBTQ) groups[32] and could translate into outreach for research purposes.

Community engagement can shape basic mechanics of a research initiative, from how permissions and consent are managed, to ensuring availability of multilingual resources, or prioritizing health literacy considerations when information is presented to personnel and participants.[29] Community engagement can also provide invaluable insight on wider-spanning components of a given research initiative, such as combating misinformation and/or misperceptions, mitigating distrust, incorporating cultural competence throughout every interaction with participants, or setting up eligibility criteria and administrative requirements that are approachable and lessen barriers for the intended participants.

Finally, the onus is on investigator teams to communicate what makes research valuable to those who participate in it, and how that value may vary across communities. Aspects such as the optimization of the return of results,[33] ensuring that the value of research participation is understood, and ensuring that the knowledge accrued during

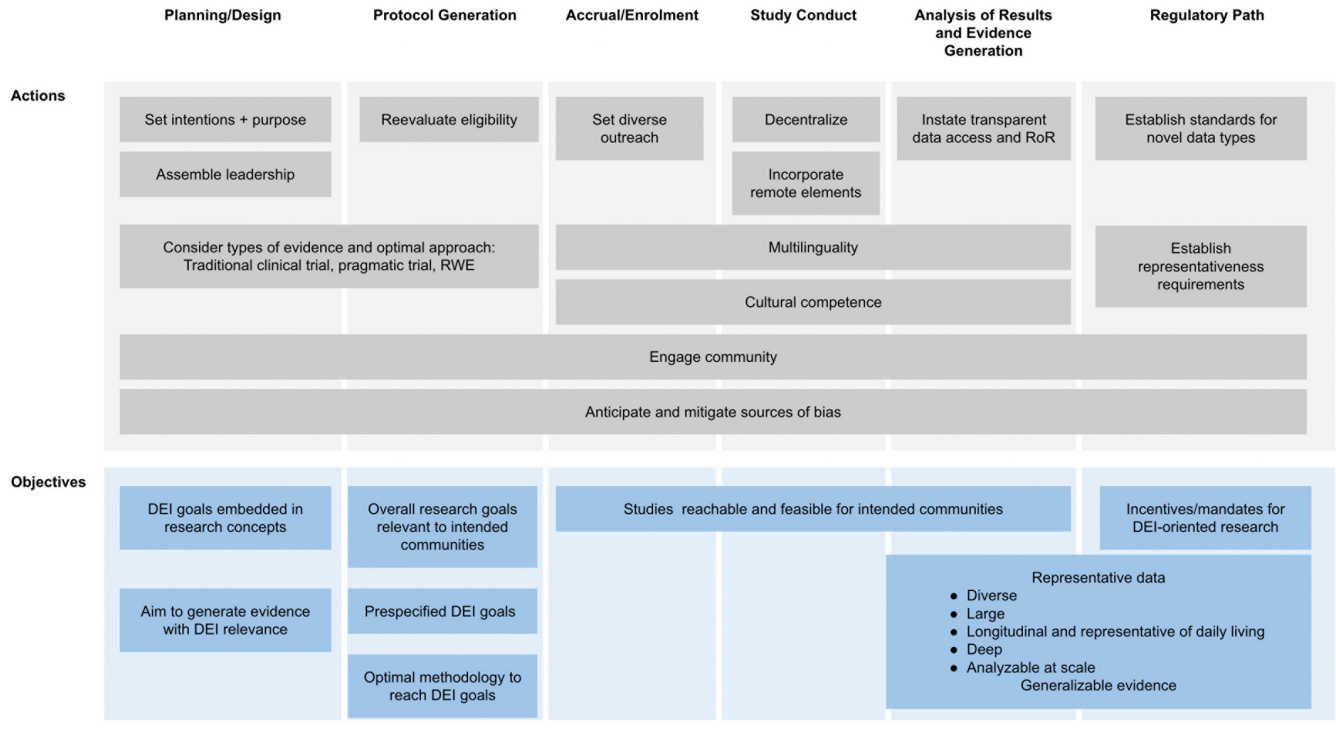

Figure 1 Summary of proposed actions for the clinical research community to improve DEI (top) and objectives that those actions are expected to accomplish (bottom).

research reverts and benefits those who made it possible, cannot be addressed with monolithic approaches and should be informed by community input. In this regard, technologies have greatly expanded the means of effective communication and engagement, but it is also true that communication is an area where community partnerships that reach patients directly can be effective. In the Project Baseline Health Study (PBHS; NCT03154346, sponsored by Verily Life Sciences), a participant survey revealed high receptiveness to receiving research results, but there was noticeable variability according to age, or sociodemographic characteristics regarding "how to" preferences,[33] which lends support to maintaining an architecture of multichannel engagement with those participants.

Diversity has to be tangible in research teams themselves, particularly at the leadership level

This will place them in better positions to drive initiatives strongly committed to DEI. The effects of this are probably twofold. By holding multiple perspectives in their midst and having a better chance at representative decision making, diverse research teams can expand their thinking and mitigate blind spots. In addition, diverse teams can probably leverage greater trust and credibility from the communities they intend to serve, under the principle that "people trust leaders who look like them." Unfortunately, lack of diversity and representativeness are known shortcomings of the clinical research workforce,[34,35] although it is encouraging to see institutions, public and private, taking steps toward closing existing gaps.[36,37] These steps can take the shape of programs with specific goals to increase the diversity of the investigator population, or wider-spanning initiatives to raise and maintain awareness of the existing gaps and identify areas of improvement.

Restrictions imposed by limits and rigidity in traditional eligibility criteria on clinical studies have to be mitigated

Participants in clinical research are defined by inclusion/exclusion criteria that may disproportionately cast aside underrepresented groups. The virtually ubiquitous restrictions around organ function deficiencies or comorbidities more prevalent among minorities are the clearest example of this. Fortunately, efforts to re-evaluate and introduce flexibility in standard eligibility criteria are underway in specific diseases, and their importance is widely recognized by all stakeholders, including regulatory authorities.[38,39] A more insidious barrier is the one stemming from enrollment bias at recruitment sites, when potential study participants are considered "at risk" in terms of loss to follow-up or overall compliance with study procedures. This type of situation can be mitigated by fostering cultural competence and reflection about personal biases in study teams and creating trusting environments to optimize participant engagement.

Recruitment methods for clinical studies can be tailored to be effective in diverse communities

Recruitment (or lack thereof) oftentimes determines the failure of clinical studies. This issue becomes larger when the intention is to enroll representative populations, where the standard recruitment tools used by sponsors (public or private) may not work well. For instance, outreach efforts narrowly centered on specific health systems or academic institutions may not touch the intended recipient communities. Ambitious initiatives, such as the "All of Us" Program[40,41] or the PBHS,[42] intend to reflect the US population, and their multipronged recruitment efforts have been commensurate with that goal. Other initiatives, such as the HERO (Healthcare Worker Exposure Response & Outcomes) Registry and HERO Together study (NCT04342806; sponsored by Pfizer), are more focused and can boost recruitment by anchoring referral and information points across target communities (in locations such as pharmacies), in multilingual platforms, and with strong remote enrollment strategies.[43] Another example is the Predictors of Severe COVID-19 Outcomes (PRESCO) study (NCT04388813; sponsored by Verily Life Sciences), where the disproportionate impact that COVID-19 had on minority populations made it critically important to ensure that a representative population was enrolled. Multilingualism was implemented across study sites, with translated study documentation (consent forms in Spanish) and Spanish-speaking clinical staff available during recruitment, to facilitate the process and mitigate concerns that potential participants may have about the quality of care they would receive. This concept of tailoring recruitment locations to known community anchors has also been applied to studies focused on LGBTQ participants.[44]

Clinical study procedures can be modernized to reduce access barriers and participation burden

The decentralization of clinical studies made possible by technologic solutions is an aspect that has garnered a lot of attention recently, undoubtedly also due to the disruptions associated with the COVID-19 pandemic. However, study teams can also consider coordinated approaches that combine remote arrangements and actual footprints to support participants who may prefer in-person interactions; in other words, the paramount consideration is to attend to participants' preferences and "meet them where they are."

The incorporation of decentralized elements in phase I–IV trials can be instrumental in fostering representativeness at two levels: opening the "playing field" to communities that for a variety of reasons (geographic, or limited material or time resources) had traditionally been left on the sidelines, and reducing the participation burden to trial participants in general. Examples of such decentralized elements include e-consent and digital medicine tools. E-consent,[45] which enables the remote conduct of consenting processes, allows for platform customization to boost engagement with study information or for individuals with specific needs; it also empowers participants to make decisions from within their familiar environment and possibly assisted by those in their care circle. Digital medicine tools[46] can enable mobile clinical trials, or substantial aspects of them. Technology can facilitate remote visits, monitoring, data collection, and analysis, vastly improving the ability of any research team to accommodate and facilitate study participation for individuals who may be geographically dispersed or have limited resources or time (due to work or family obligations) for transportation and commuting.

Yet, there are certain research aspects that require in-person interaction, such as adverse event management and documentation, or tests. Teams can consider intermediate remote approaches

that unlock untraditional study sites, such as community centers, churches, or local pharmacies. Approachability at this level can also improve trust and engagement. Interestingly (unfortunately), the COVID-19 pandemic has offered a crash-testing model for some of these approaches, such as the use of pharmacies as recruitment points for the HERO registry and HERO-together study, or the upsurge in telemedicine in general.

To optimize this modernization, some factors already discussed in this article have to feed into one another—namely, meaningful community engagement is critical to understand the real-life issues that potential participants face, and only that understanding can inform the optimal deployment of novel tools in a clinical study to solve those issues.

Another issue that will require community-specific solutions, as we aim to generate evidence generalizable across the socioeconomic spectrum, is the elimination or mitigation of financial and/or administrative barriers to clinical trial participation that may not be actually relevant. Perhaps the clearest example are requirements around insurance, employment, or residency documentation, which may represent insurmountable barriers or major deterrents for potential research participants. It behooves investigators to evaluate to which extent those elements may (or may not) be necessary for a given study. It is also important to ensure that potential participants have accessibility to studies, whether or not they are tied to specific health systems or clinical trial sites. The common traditional scenario of clinical studies based on large academic institutions may be too limiting and exclusionary; as mentioned above, the COVID-19 pandemic has expanded our views of what research sites look like, with successful utilization of diagnostic testing sites or pharmacies for research engagement.[47]

BEYOND STUDY TEAMS: EXTERNAL FACTORS CONTRIBUTING TO DEI IN CLINICAL RESEARCH

The efforts outlined above would largely stem from the study teams and organizations, but other players in the research landscape can also contribute to the generation of richer evidence, less biased toward single groups who have had a dominant presence.

Regulatory requirements and expectations related to diversity in clinical research

One area that will define the shape of clinical research looking forward is the realm of regulatory requirements and expectations related to diversity, which are still evolving and are important for achieving broad, durable progress. Regulators can create an environment that favors increased diversity in clinical trials in two ways: (i) by developing and applying regulatory requirements for the inclusion of diverse groups of people in clinical trials intended to support regulatory decision making, including groups that have been historically underrepresented in clinical research; and (ii) by clarifying the regulatory status and expectations for the use of evidence generation tools that can increase access to clinical studies by diverse groups. The US Food & Drug Administration (FDA) and other regulatory bodies have made progress in both of these areas. Ongoing progress will depend, in part, on the ability for these regulatory bodies to use better metrics to evaluate the diversity and representativeness of research used to inform regulatory decisions and then take targeted action to ensure appropriate standards are met.

Medical product regulatory bodies have become more explicit and assertive about requirements for the diversity of participants in clinical trials that are intended to support regulatory decisions. There is broad consensus among regulators internationally that clinical trials supporting medical product development should include participants from diverse populations that will receive the product in clinical practice.[48] These expectations have been rooted primarily in clinical concerns that adequate diversity in clinical development programs is needed to understand differences in the safety or effectiveness profile for a product in different groups (see, e.g., Collection of Race/Ethnicity Data Guidance[49] or Japan's Pharmaceutical and Medical Devices Agency (PMDA) expectations for confirming safety and effectiveness in the Japanese population[50]). In the United States, the FDA has implemented multiple measures intended to understand and enhance the representativeness of clinical trials submitted in support of regulatory review of medical products, and expects the evidence submitted in support of the products it regulates to be representative of the clinically relevant populations for the product use.

Data collection and transparency about the actual representation of diverse groups in clinical research have created a greater understanding of the problem of diversity in clinical trials that support regulatory decisions.[51] The FDA mandates the reporting by sponsors of data on the breakdown of clinical trials by age, gender, race, and ethnicity (see Collection of Race/Ethnicity Data Guidance[49]). These data paint a complex picture. Reporting to the FDA on the race and ethnicity of participants at US clinical trial sites indicates that the racial and ethnic representation varies widely by therapeutic area.[39] Groups other than White participants are notably underrepresented in trials for cardiovascular diseases, compared with US census rates for those groups, while minority groups were generally overrepresented in infectious disease trials.[52]

In 2022, the FDA proposed a more intentional, standardized process for incorporating diversity into the planning of clinical studies by recommending that medical product developers submit a "Race and Ethnicity Diversity Plan" to the FDA that will detail how the developer plans to enroll representative numbers of participants from underrepresented racial and ethnic populations in the US.[53]

Yet, efforts to increase diversity in clinical trials are limited by the data used to measure the diversity in clinical trials. The data on diversity in clinical research that is currently available have significant limitations. For example, the FDA's demographic reporting and diversity planning requirements rely on a limited set of self-reported race and ethnicity categories that are socio-geographic constructs, rather than scientific constructs.[28,54]

Other demographic, socio-economic, and geographic information sources, beyond the limited information currently available to regulators about age, race, and gender, could help regulators evaluate additional dimensions of clinical trial diversity. For example, information derived from geospatial data could allow the FDA to assess the geographic diversity of participants in a clinical study, including to what extent participants were located in rural or urban areas or areas characterized by high or low social vulnerability or deprivation. There are significant scientific, technical, and

policy questions about how new sources of demographic, or socioeconomic information should factor in decision making, but progress in this area could unlock greater representation in the clinical research relied on by regulatory agencies.

In addition to actions that are directly targeted to increasing diversity in clinical trials, regulators can take indirect steps to make the clinical research environment more conducive to diverse clinical studies. As discussed in this article, the accessibility of a clinical trial to diverse participants is an important factor in driving greater representation. Regulatory requirements are important for enabling appropriate use of tools like remotely conducted informed consent and remote data collection technologies which, if implemented thoughtfully, can facilitate participation by diverse participants who may otherwise not be able to physically reach a central study site. A frequently cited example is electronic informed consent, which allows a participant to enroll remotely in a clinical study.[55] Regulators also set expectations for the use of digital tools like wearable sensors to collect physiological or behavioral data remotely for use in a clinical study. The FDA has made significant progress describing their technical and scientific expectations regarding the use of such tools to generate clinical evidence.[56] While the use of remote sensors in clinical research is still limited, this is likely to change as the tools gain greater acceptance by regulatory reviewers.

Identifying attributes and expanding sources for representative and robust evidence

Representativeness in traditional phase I–IV clinical trials can improve to generate better evidence, but the larger research community (by setting standards or creating technical capabilities) can propel complementary and more representative evidence approaches to come of age.

First, several features can make complementary data sets particularly valuable to enrich the evidence base and better serve clinical decision making for diverse populations:

- *Diverse as the populations of interest* (for example, All of Us,[40,41] or the PBHS[42]), a pursuit that will manifest itself in accrual efforts or engagement approaches.
- *Large enough and with analytical power* to support robust decision making.
- *Longitudinal and representative of everyday individual lives*, in addition to data elements collected via the health system. Data collection can lean on routine clinical platforms/electronic health records and/or via mobile clinical trial systems.
- *Deep*, with the genotypic/phenotypic reach to inform precision medicine (for instance, clinico-genomic databases,[57] or richly sourced data models such as the ones in the PBHS,[42] or with ambitious data plans to generate sophisticated risk stratification models, such as Presco).
- *Enabled for data analysis and processing at scale*, since the large data amounts collected will require commensurate applications and adequately validated artificial intelligence to generate high-grade evidence (see below).

With all these features in mind, evidence generated from observational/real-world data (RWD) or pragmatic trials[58] can provide the type of evidence that clinical trials cannot. Contributions from the technology and analytic fields have helped this space mature and develop the potential to address some shortcomings from trial-based evidence, as has been acknowledged by regulatory authorities.[25,59–61] Being intrinsically rooted in routine care, these studies can elevate DEI by accruing sizable cohorts from populations underrepresented in traditional trials. RWD, in particular, can provide insights on the whole all-around performance of medical interventions for all patients across the spectrum, from high-resource to low-resource underserved settings. RWD can also trace longitudinal patient trajectories, shedding light on the full delivery of complex care across the continuum of diseases or conditions that a patient may experience. Pragmatic trials, on the other hand, can provide methodological flexibility for research that may require intermediate balanced approaches, for instance minimizing analytical bias present in RWD studies, and still expand beyond the constraints of traditional clinical studies.[62]

Evidence generated by digital technology wearables represents another avenue likely to push the traditional clinical research boundaries, and it is the ultimate approach to decentralization and "meeting study participants where they are." These technologies can enrich data sets that still rely on more traditional clinical measurements, or increasingly be the sole basis of full studies. Apart from the advantages of decentralization and minimizing study participation burden, these approaches allow for high granularity in data collection at the individual level, potentially delivering on the promise of individualized evidence toward personalized medicine.[63]

KEY CONSIDERATIONS FOR A NEW LANDSCAPE

There are key considerations that should be top of mind in the incorporation of (relatively) novel approaches and types of evidence into clinical research:

Trustworthiness, integrity, and transparency

Data collection and the infrastructure for data management has to be trustworthy and meet standards for privacy and security. Transparency around this aspect is of utmost importance as we have acknowledged that one of the pending issues bringing underrepresented communities into the fold is that of mitigating distrust.

Data processing and handling has to be rigorous and transparent, and "return of results" and external data access have to be key considerations to the extent possible. A special item of interest in the realm of DEI is the minimization of bias occurring during processing, particularly in the deployment of artificial intelligence for these tasks (see below).

Vigilance about hidden biases

As health data are digitized, the prodigious volume of health record, diagnostic study and imaging, laboratory and genomic, and biometric data being generated is spawning considerable research to create algorithms to assist in processing and synthesizing these data into clinically actionable information. When an individual is expected to generate hundreds, if not thousands of terabytes of health-relevant data in a lifetime,[64] algorithms must inevitably

play an important role in improving health; yet this promise is also inevitably accompanied by risks. As Obermeyer *et al*. reported in 2019,[65] an algorithm used to allocate care management resources to patients did so inequitably. White patients received more resources than Black patients even when they had lower burden of disease.

At this point it is worth defining an algorithm. To quote from a well-known textbook on algorithms, "An algorithm is any well-defined computational procedure that takes some value, or set of values, as input and produces some value, or set of values, as output. An algorithm is thus a sequence of computational steps that transform the input into the output."[66] Therefore, an algorithm can range from a simple arithmetic operation to a deep neural network.

In statistics and machine learning, algorithm training depends on the originating data and the use of those data. For example, with the algorithm described above, racial bias was both embedded in the data and in the assumptions made about the data. By using healthcare spending as a proxy for disease severity, its creators failed to account for systematic differences in access to and utilization of health care. This analysis raises core questions about DEI when researching algorithms for clinical use: What outcome does one hope to achieve? And can the outcome data intended for use be disentangled from social constructs such as race? How do researchers identify bias embedded in data?

While addressing the outcome question, a critical issue is how one formulates the problem. In other words, "It requires various forms of discretionary work to translate high-level objectives or strategic goals into tractable problems, necessitating, among other things, the identification of appropriate target variables and proxies. While these choices are rarely self-evident, normative assessments of data science projects often take them for granted."[67] The "taken for granted" part is often a stumbling block for researchers. One would expect that most do not set out to build an unfair algorithm, but end up unknowingly or naively doing so by formulating the problem without accounting for the possibility that the algorithm will treat groups inequitably. This problem is particularly important with algorithms because technology allows them to scale more widely than individual clinician bias. Friedman and Nussenbaum note that the nature of computer systems are such that "hidden biases can be widely dispersed, leading to pervasive (but unrecognized) harms."[68]

We want evidence to be of high quality, reliable, robust, and generalizable, and for that, we need to collect representative data. There are other examples that reflect how the lack of representativeness in foundational data for the development of digital tools may ultimately lead to wrong practices.[69] Data captured by sensors can be hopelessly biased if calibrated with only one physical paradigm in mind, for instance, when skin pigmentation affects the accuracy of readouts, in a clear example of a representativeness failure; as a result, the evidence derived from unrepresentative data has led to wrong clinical practice patterns for specific segments within a diverse patient population.[70] The development of these technologies has to contemplate the diverse populations where they are to be deployed.

Because algorithms often will be deployed into a "live" production setting, an additional consideration is planning for continuous monitoring of algorithms after deployment. Issues such as data drift—where the data an algorithm "sees" differ substantially from the data on which it was trained because of, for example, seasonal trends, or changes in the population of interest—require that algorithm builders assess whether the algorithm is performing to their expectations when viewed through the lens of DEI variables. There is active interest in "fairness toolkits" for machine learning workflows,[71] and adapting them to dynamic and real-world environments remains an active field of inquiry.

Optimizing the participant experience and engagement throughout

While we aspire to a modernized research environment, there are basic unavoidable operational and mechanical aspects to study participation, such as screening and event scheduling, for which engagement has to be optimized for the diverse communities where participants come from. The principles outlined above, of engagement, and management attentive to the needs of the individual participant should apply to all operational aspects of a study, regardless of novelty. For instance, the PBHS relies on multichannel participant communications, via e-mail, but also via wearable device to maximize engagement; the ease of user interfaces and the democratization of access has to be at the forefront of how those communications are developed to foster engagement.[42] Yet, considerations around ease of engagement have to be balanced with the principles outlined at the top of this section of trustworthiness, integrity, and transparency in any user interaction. Engagements with participants can also be oriented toward bidirectional communications (the recurring theme of creating infrastructure fit for *a dialog with* participants, rather than *a lecture to* participants) with room for reciprocity, where participants receive value back, and for agency, where participants are enabled to contribute to decisions.

Institutional and organizational accountability

For all the aspects reviewed in this piece, accountability within organizations from leadership onward is critical to maintain effective and meaningful cross-sector partnerships to fill DEI gaps. For instance, the PRESCO study intentionally sought partnerships with institutions specifically serving minority populations. That intentionality, and the specific tactical approaches implemented at the recruitment sites, resulted in successful enrollment of African American (one-third of the cohort) and Hispanic (another third) participants. This requires a team effort where technical and human components are layered effectively toward optimizing study goals and representativeness.

As indicated in some previous points, addressing unconscious, inherent, and systemic bias at all stages and levels (human and technological) should be a constant throughout research efforts. It is worth remembering that any commitment to DEI begins with those building the basic research tools and passes through the extent of DEI in healthcare organizations conducting the research. Deficiencies in these foundational blocks will probably lead to lack of generalizability of results, and ultimately a failure to deliver on the best possible outcomes for a diverse population.

LOOKING AHEAD

What should we expect from the research community as we chart a better path to increase DEI in our efforts?

The concept of *Equitable Research Design* remains aspirational today, but could become a foundational principle, and any research effort has to humbly self-examine and curtail overly broad assumptions at the inception stage. This idea rests on the pillars mentioned earlier in this piece: intentionality in research goals and conduct, ever-present community engagement, ensuring that teams and leaders embody diversity, maintaining a keen and open-minded eye in the areas of recruitment and eligibility, and toward the reduction of participation barriers in general.

Measurements of success also have to contemplate a mind shift. As we become more insightful about our seemingly neutral status quo, we realize that it maintains many of our societal biases. Intentionality at this level, too, to directly acknowledge and address differences among groups of concern will be key. Successful research will be the one that specifically sets an analytical framework to gain a robust understanding of health outcomes across the entirety of a diverse population.

Similarly, we now know that many existing assumptions can be the starting points for insidious biases. The practice of constant re-examination of predicates and assumptions in data modeling and algorithm development has to shift from being a source of isolated examples to becoming a general research rule.

As most of these represent new organizing principles, research institutions and organizations will have to remain internally committed, devoting attention and resources to these shifts, and continuously vigilant to assess their own performances. Externally, the commitments of these organizations have to be based on transparency and on receptivity to the demands of the landscape around them. Those demands may be "societal at large," or specifically applicable to discrete research initiatives. In this vein, the ongoing evolution of the regulatory environment will be a critical determinant to increase access to clinical research and diversity in clinical studies. The actions by the FDA to make demographic information for clinical studies more transparent have been a good start and underscore the need to develop better data and metrics to evaluate the diversity in the clinical studies submitted for regulatory review. Better information could, in turn, help regulators and medical product developers take more targeted actions to increase the accessibility and representativeness of trials—both at the individual study level and through the development of broad regulatory policies, including those that support the appropriate use of tools that make clinical studies more accessible.

In summary, improving the status quo of DEI in clinical research will require concerted efforts by all stakeholders in this environment, from regulatory authorities to lead researchers and operational personnel. Sir William Osler was noted to have said, "It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has." This is a reminder, when science necessarily involves reduction, that one needs to widen the objective (lens) from pathophysiology to people and populations. As we make progress in our knowledge, improvements in health care cannot be limited to certain populations that benefit from the spearhead of that progress, but they have to reach the wider spectrum of a diverse society. Today, there are notable gaps and disparities across that spectrum, and this is a situation about which the research community should not be complacent. We can use tools to make our research more representative, which, at their core, are means to inject that reminder to bring a wider perspective into our work. Within each segment of the research path, there are specific actions that can be taken to increase DEI, and there are quantifiable objectives about the improvements that can be expected.

Recent technological advances have opened the door to multiple mechanisms that can revolutionize research execution, allowing expanded reach, decentralization, and flexibilization. Yet, tangible improvements will necessitate research organizations to show sustained commitment to DEI as an intentional goal that warrants significant resource investment, to exert self-awareness and vigilance about biases (in the human and technical realms), and to show accountability and willingness to engage in leveled approaches to communication and community interactions.

ACKNOWLEDGMENTS

The authors wish to acknowledge Jay Arora for his contributions to this piece, and the writing and editing support from Julia Saiz, from Verily Life Sciences.

FUNDING

No funding was received for this work.

CONFLICTS OF INTEREST

All authors (V.W., J.B.F., E.S.H., J.L.M., and A.A.) report employment and equity ownership in Verily Life Sciences. In addition: VW reports membership in the board of the Harvard Medical Faculty Physicians; ESH is the founder of KelaHealth and Clinetic; JLM reports membership in the board of Danaher; APA reports membership in the boards of directors for EQRx, Inc. (publicly held company) and Georgiamune LLC (privately held company), and personal investments in One Health and Iterative Scopes.

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