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Title: Inclusionary trials: A review of lessons not learned

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Abbreviations: STOP COVID-19 CA, Share, Trust, Organize, and Partner to STOP COVID-19 California Alliance

Abstract

The COVID-19 pandemic revealed weaknesses in the public health infrastructure of the United States, including persistent barriers to engaging marginalized communities towards inclusion in clinical research, including trials. Inclusive participation in clinical trials is crucial for promoting vaccine confidence, public trust, and addressing disparate health outcomes. A long-standing literature describes the value of community-based participatory research (CBPR) in increasing marginalized community participation in research. CBPR emphasizes shared leadership with community members in all phases of the research process including in the planning and implementation, interpretation, and dissemination. Shared leadership between academic and industry with marginalized communities can assist with inclusive participation in vaccine trials and increase public trust in the development of the vaccines and other therapies that are used during public emergencies. Nevertheless, epidemiological and clinical research do not yet have a strong culture of community partnership in the scientific process, which takes time to build and therefore may be difficult to develop and rapidly scale to respond to the pandemic. This article outlines practices that contribute to a lack of inclusive participation and offers steps that trialists and other researchers can take to increase marginalized communities' participation in research. Practices include planning for community engagement during the planning and recruitment phases, having regular dialogues with communities about their priorities, supporting them throughout a study, and navigating complex structural determinants of health. Additionally, we discuss how research institutions can support inclusive practices by reexamining their policies to increase participation in clinical trials and instilling institutional trustworthiness.

INTRODUCTION

According to the Food and Drug Administration (FDA), clinical trial enrollment should reflect the diversity of persons likely to utilize a drug or intervention (1). In their November 2020 report on diversifying clinical trials (1), the FDA repeatedly warned that homogeneity among clinical trial participants limits adequate evaluation of the "benefit-risk profile" (1, p. 4) among persons who are likely to utilize a drug or intervention and may diminish the knowledge gained on safety and effectiveness. The FDA's warning is especially salient given the acutely relevant role of adverse structural determinants of health—such as structural racism, education access, restricted economic mobility—on healthcare access, disease incidence and mortality, and health disparities (2-5). Restrictive eligibility practices (e.g., unjustifiably excluding persons with complex health experiences like obesity, HIV) and not accommodating structural barriers (e.g., not addressing socioeconomic barriers like caregiving responsibilities, lack of transportation) are emblematic of the implicit biases and institutional racism that underlie the policies and procedures of academic, industry, and other scientific institutions (henceforth referred to as research institutions) and sustain science's role in structural racism (6,7). Consequently, a closer examination of inclusionary and exclusionary practices in clinical trial design and implementation as well as long-standing clinical research practices and their implications for equity, diversity, and inclusion in clinical research is needed (8). This article builds on a robust body of literature that stresses the urgency of inclusive trials (i.e., trials with enrollments that reflect diversity of social groups and personal experiences) for promoting population health and addressing health inequities (9-14).

Adequate diversity among participants in clinical trials has persistently eluded clinical research studies. A not-so-distant history informs us that prior to the historical period known as integration (1960-80s), Black, Indigenous, and Latinx/a/o people and other communities that have been historically marginalized (henceforth referred to collectively as marginalized communities) were excluded from clinical research or were victims of experimentation and research misconduct (15-17). Literature since the 1990s has warned of the consequences of lack of representation in clinical trials for disease outcomes (18). These warnings have been coupled with efforts by grantmaking institutions like the National Institutes of Health in 2001, and the FDA more recently in 2020, to strongly encourage clinical research studies to engage in more

inclusive research practices to diversify trial participation (1,19). Despite these calls, inclusive research participation continues to lag. Trends in pharmaceutical trial participation between 2015-2019 indicate Black people make up 7% of pharmaceutical trial participants, Indigenous people make up 1%, Latinx/o/a people 13%, and Asian people 11% (20). The overwhelming majority (76%) of drug trial participants identify as White.

Pre-existing trends in the lack of diversity in clinical trial participants was evident in recent vaccine trials for SARS-CoV-2 (COVID-19). White people made up 82% and 80% of participants in the Pfizer-BioNTech and Moderna vaccine trials, respectively (21). Black (9.8%,9.7%, respectively), Indigenous (0.6%,0.8%), and Asian (4.4%,4.7%) people made up less than a quarter of participants for both vaccine trials (21). In the United States (US) alone, the anticipated population needing vaccination is much more diverse than the Pfizer-BioNTech and Moderna vaccine trial samples indicate. The composition of racialized and minoritized (i.e., Indigenous, Black, Asian, Latinx/a/o, etc.) participants did not reflect the disproportionate impact of COVID-19 within such groups in the US (22). Despite being at greater risk of the novel virus due to structural racism (23-25), many racialized and minoritized communities questioned the effectiveness and safety of the vaccine for them—in part, because of concerns about adequate representation in the trials (26-28). The disconnect between a lack of diversity in vaccine trials and the racialized and minoritized populations the vaccine was to serve occurred despite robust literature from over a decade highlighting evidence-based practices for inclusive research participation (29-31). This disconnect demonstrated yet another instance of the pandemic revealing what was already there: the persistence of structural barriers in clinical research and in the knowledge production of science.

EXCLUSIONARY PRACTICES

Lack of diversity in clinical trials is a persistent problem that undermines the success and translation of clinical and other health research into real world settings. Despite recent overemphasis on vaccine hesitancy, we argue a lack of diverse representation in vaccine, pharmaceutical, and other trials is largely due to barriers built into the infrastructure of scientific research. These practices include: lacking consideration for how certain eligibility criteria may unjustly and disproportionately exclude certain groups, placing trial sites in

settings convenient to researchers yet often inaccessible to marginalized groups, having monolingual English-speaking staff and materials thus making it difficult to participate for those for whom English is not the primary language, providing rigid and complex consent and documentation to groups with challenges to health literacy, failing to acknowledge or limitedly addressing barriers to participation (e.g., transportation, childcare). And, in the case of COVID-19 vaccine trials, lacking quarantine support for those who may contract the virus.

Exclusionary practices in clinical research are set at the institutional level when policies are developed solely to protect and serve the interests of the institution over the communities it serves. Such exclusionary practices are reinscribed when researchers who work within research institutions fail to seek, be aware of, and/or devalue community input. These practices perpetuate discrimination and do not prioritize marginalized and under-resourced communities, but instead reinforce community distrust in research, science, and academic institutions (32).

Centering ourselves and not the community

Despite the emphasis on community engagement and cross-sectoral collaborations (33), partnership with community groups and stakeholders continues to remain underutilized in clinical research (34). This may be due to educational curricula that less often incorporates content helping scientists gain competencies in community engagement and community partnerships to improve science. There are also assumptions built into the science itself that prevent consideration for engaging community. Many scientists may assume inclusion is important further down the research road after Phase 2 trials. This perspective doesn't consider that samples used in-vitro research and early clinical phases do not reflect the universe of exposures and experiences that are needed to adequately understand scientific mechanisms. The pathway to intervention or drug discovery is built on the assumption that scientific processes will result in efficacy across all diverse communities. However, if diversity in participation is not achieved in the development of the science, from the building of research questions to the samples used to explore salient mechanisms, then the translation and applicability of clinical research may be undermined.

Researchers engaging marginalized communities (henceforth referred to as scientific partners) may wrongly take the position that expertise resides solely within research institutions and the contributions of communities are of lesser value. We reify this perspective when we do not partner with communities during the research design stages. Even when we do collaborate, we limit their contribution to recruitment and compensate community organizations and leaders too little for the expertise they provide. The centering of scientific partners' ideals over community perspectives is evident in the types of studies we implement and the ways we convey information to communities and patients (35). For example, we can acknowledge that structural determinants like segregation and gentrification have broadened the physical distance between research institutions and under-resourced communities. However, in designing a study, we will fail to provide flexible study hours, adequate transportation reimbursement, and other support while participants may have to commute many miles to multiple appointments on workdays to take part in a study we believe is vital to their well-being. We contribute to inequities when we create study documents in one language when those affected by the disease under study speak many and when we do not recruit from settings where more marginalized groups receive their healthcare. We design research that implies a sentiment of "they will come to us" as opposed to leveraging our scientific privilege and centering the needs of the communities we serve through science.

Institutional policies that contribute to the exclusion of marginalized populations

Numerous exclusionary policies limit the translation of research findings to communities that are often disproportionately affected by the condition of interest. For example, institutional review boards (IRBs) implement restrictive policies around incentives which do not adequately account for the time (e.g., lack of paid time off) and effort (e.g., transportation costs, travel from rural settings to academic health centers, past negative experiences in the health care system, distrust of research) that is truly entailed in research participation. Structural policies (e.g., federal regulations) may drive institutional barriers, including regulations about how to offer remuneration that can exclude participants from research. For example, policies that require participants to show identification or provide social security numbers for reimbursement can exclude participants without documentation, and policies that require remuneration in the form of checks deter

participation for those without bank accounts who face fees to cash checks. Lengthy, confusing, and English-only consent processes can exclude participants with cognitive or physical disabilities, challenges with health literacy, or limited English proficiency (note almost one in five US residents speaks a language other than English at home) (36).

Individuals with comorbidities are sometimes excluded from participation to avoid grappling with the influence of these and other variables on trial outcomes (1). Research on structural racism shows that marginalized communities were forced into geographic areas with limited resources and environmental pollutants that have shaped their health experiences with many chronic conditions (37-39). For example, food deserts and green space-free urban neighborhoods are associated with overweight/obesity, chronic stress, and community-level trauma (40-42). Exclusion of people with comorbidities from studies implicitly decreases the inclusion of racialized and minoritized groups as well as other marginalized populations in multiple ways. Similar implicit processes of exclusion occur in common statistical analyses when sociodemographic variables that are reflective of structural determinants (i.e., structural racism, education access, restricted economic mobility) are adjusted for instead of allowing them to influence the outcome as would occur in a natural setting (43). Thus, the exclusion of individuals with comorbidities and the exclusion of the impact of structural determinants of health in our analytic models are not routinely incorporated into the design and implementation of clinical trials despite their utility when examining causal factors in populations with diverse experiences.

Bureaucratic processes in research institutions can also prevent meaningful partnerships with community-based organizations and groups (i.e., community partners). Onerous invoicing processes can require community partners to pay for expenses out-of-pocket and be reimbursed later, and the amount of paperwork required for subcontracts can deter under-resourced organizations, whose core mission is not research, from engaging in science. Thus, only community partners with financial resources and substantial staffing may be able to engage research institutions. During the COVID-19 pandemic, grassroots community partners, including promotoras or community health workers, carried the load of education, testing, and vaccination serving in essential roles as trusted messengers in the community. Yet promotoras, who may not

be US citizens, often face barriers to salaried payments for their services and delays in reimbursement for their labor through fiscal sponsor organizations. The widespread experience of COVID-19 could have inspired the use of pragmatic vaccine trials instead of traditional clinical studies where participants travelled to research institutions. These and other practices are exclusionary and require resolution.

Unfortunately, this is far from an exhaustive list of exclusionary practices of research institutions. Many of the aforementioned exclusionary practices rely heavily on traditional top-down research procedures, institutional restrictions, and a lack of innovation in envisioning a more inclusive research paradigm. Going forward, it is possible to conduct clinical trials differently. We can implement reflexive processes that uproot exclusionary policies and continuously examine research practices and IRBs for bias. In short, we can and must do the work.

One way of combating the individual, institutional, and ethical barriers to engage marginalized communities fully—rather than solely to increase recruitment into clinical trials—is for communities to partner in the development of a drug or device during a randomized control trial (44,45). An advantage of such a partnership is that community input can ensure external validity. Such practices improve scientific inquiry, empower communities, and increase trust between marginalized populations and clinical investigators and their respective institutions. Bench scientists, translational investigators, and clinical and public health researchers and practitioners, and others must adopt a community-centered approach to research to ensure the translation of our work and to achieve health equity.

INCLUSIONARY PRACTICES: COMMUNITY-BASED PARTICIPATORY RESEARCH

Community-based participatory research (CBPR) is an approach that integrates community as an elemental part of the research process (45). "Community" in this context refers to a group that shares social ties and perspectives as well as engages each other geographically or socially (46). Through shared decision-making and collaboration, a CBPR study decenters the needs of an institution and its researchers and centers the needs of the community in an equitable way (47-49). CBPR is characterized by four parts: community engagement, partnership, action, and change, which we will discuss below.

Community engagement

Community engagement refers to continuous and bidirectional sharing of information and resources between scientific and community partners throughout the process of research development (e.g., identifying appropriate research questions and designs) and implementation (e.g., instrument development, methods selection, and recruitment strategies) (47). It is a process that thrives on localization of efforts, ideas, and relationships. Scientific partners, such as academic institutions, may share up-to-date scientific information on a disease or condition to which community partners offer insight and feedback. Community partners, such as community-based organizations, may share information on structural mechanisms that contribute to disease incidence, prevalence, or mortality, an understanding of which is vital for the scientific community. Mutual recognition of expertise supports the coproduction of ideas, the selection of appropriate methods and approaches, and the identification of research questions valued by all parties (45,50).

Information sharing and respectful listening do not happen overnight. Rather, establishing the foundation of trust upon which such sharing becomes possible is a multi-stage process in which both parties evaluate each other. The scientific partner may evaluate the community partner's capacity to collaborate with them in scientific endeavors and the community partner may in turn evaluate the former to assess the potential for further harm due to structural racism and other biases (51). Just as the actions of community partners may reflect upon a community, so do the actions of a researcher on their institution, and instances of disrespect, disregard, or mistreatment by researchers may have long-lasting effects (52,53). Consequently, it is incumbent upon scientific partners to initiate community engagement as early as possible to allow for the time needed to thoughtfully build sustainable connection and trust through actions that display the institution's willingness to learn and grow through the relationship.

Partnership

The concept of partnership within community and global health has come under strong critique, largely due to the many ways the concept has been employed and the general lack of attention to power dynamics within community/scientific partnerships (54-57). Green and colleagues argued over 20 years ago that community/scientific partnerships are essential to addressing structural determinants of health because no single agency has the resources, access, or trust-centered relationships necessary to address the wide range

of public health problems (57). Since that time, public health researchers have worked to inform the structure and evaluation of said partnerships (58). With the goal of supporting *partnership synergy*, collaborations that lead to the creation of new and valuable processes, insights, and outcomes are possible through sharing of individual skills, perspectives, and resources (59,60).

A challenge to community-based partnerships is the "murky space" between theory and practice (61-63), or the distance between ideal and reality. Partnership structures such as Community Advisory Boards (CABs) help address this gap by providing oversight of the collaboration (46,59). Additional approaches strengthen community partnership including continued presence in the neighborhood or locality which the partnering organization serves, "showing up" to community events, and responding to requests for information or support. Prolonged engagement and participation demonstrate that the scientific partner is committed to the wellbeing of the community—a commitment which serves as the cornerstone of partnership.

Partnership is necessary to ensure the proposed intervention addresses community needs, that the intervention or pharmaceutical will be useful to the community of focus, and that those committing time and effort will benefit from the research endeavor. Partnership is not a barrier to the creativity and innovation inherent in clinical trial research. To the contrary, partnering with community organizations and populations of focus and incorporating their experiences and concerns within an intervention or pharmaceutical trial has the potential to push investigators to rethink research design to ensure that the priorities of such populations are addressed. At times doing so requires the kind of out of the box thinking we value in science. Partnership is not about diversifying participation in one clinical trial—rather, it is a practice that must be regularly engaged to ensure continued participation as well as health equity.

Action

Unique features of CBPR include the improvement of health inequities and the explicit value of action for social justice (64,65). While traditional research products (e.g., intervention development, academic publications) are still needed and pursued, CBPR calls for a higher standard in terms of action and benefits to the community at-large and to those involved as community partners (66). Key strategies for ensuring

beneficial short and long-term outcomes must reflect communities' cultural ways of knowing and being, build on community assets and capacity development, and include actions that are informed by community priorities due to the structural determinants underlying their health experiences (67).

During the COVID-19 pandemic, existing health inequities (e.g., in the prevalence of comorbidities associated with morbidity and mortality from COVID-19), lack of access to quality care, and overrepresentation in essential jobs created a complex picture with negative consequences for marginalized communities that are still to be rectified. Clinical trials often did not account for this array of issues and institutions were not trusted by impacted communities as having their best interest in mind. When community engagement is focused on recruitment only, there is lack of explicit policy or action benefit to marginalized communities—and often even to research volunteers, particularly those in control arms—in addressing underlying root causes of morbidity and mortality. Coupled with the barriers to participation previously discussed, the implied message was that research institutions and pharmaceutical partners were out of touch with the lived experiences of the individuals and communities they were recruiting. With a CBPR approach, action involves the co-designing of research that will contribute to change for communities in prioritized areas (68). Therefore, it is critically important to understand the experiences and concerns of communities to eliminate injustices within and outside the research arena and to reduce health inequities.

Change

Many scientific partners fall short on co-creating change in communities. We may produce research with community partners but stop at publishing manuscripts and attending conferences with them. While this is the currency that ensures scientific research jobs—and those jobs ensure we do more community-centered work—traditional science is not the only way to promote meaningful change. Change is a gradual process, and it is unlikely that one research project will solve the issues within a community, particularly the long-standing impacts of segregation, lack of access to quality care, lack of social and economic mobility, and other issues that are key in the development and maintenance of health inequities (69). However, continued engagement with communities across multiple projects spanning the translational spectrum of research has higher chances of addressing core issues compared to single projects. Thus, long-term commitment is needed

to meaningfully produce science with real world implications and to act on research findings. Consequently, scientific partners should consider building interdisciplinary teams with clinical scientists, public health researchers, social scientists, community organizers, policy analysts, social workers, and others to ensure the span of priorities of communities can be served alongside the science. Although there is a grave need for the investment of research institutions in community partnership and engagement to sustain social change.

INCLUSIONARY TRIALS

We have outlined examples where exclusionary practices lean on discriminatory actions related to who can participate in clinical research. We also discussed evidence of how CBPR can be an effective strategy toward ensuring inclusivity in clinical research. In this section, we conclude with recommendations for promoting inclusionary clinical trials.

Provide community benefit

First, we must discontinue our ahistorical approach to research where we steer clear of acknowledging or discussing the historic abuses and research misconduct that has occurred. Indeed, great importance lies in the ability of researchers and institutions to both acknowledge and be transparent about past and ongoing injustices which have disproportionately affected marginalized communities (43). Benefiting communities also encompasses partnering with them in ways that strengthen community capacity and agency. This partnership includes hiring community health workers, community organizers, research coordinators, and other research staff from the communities we partner with. Furthermore, benefiting the community includes the utilization of CABs in clinical trials and hiring social workers and patient navigators to support participants for whom structural determinants impede their participation in a study. In Table 1, we summarize how a trial can be designed to offer community benefits including increasing knowledge and access to trustworthy information, building trust in research, strengthening community access to resources, and building community capacity. Providing community benefit is akin to reducing and eliminating external barriers to research, thus, this reframing may be useful for scientific researchers seeking to convince their institutions and funders to do more.

Reexamine policies and procedures. Challenge norms. Shift paradigms.

To rid our institutions of structural bias requires dismantling harmful values espoused and demonstrated by research institutions. We need to engage in practices that build trust: from the expansion of funding timelines to account for time needed to build community partnerships, to more equitable budgetary practices that allow for culturally-responsive recruitment strategies (e.g., radio and social media advertising, return-of-value events at the end of the study period, promoting investigators who conduct CBPR). Instead of restricting the roles of community in our research, we should mold our research institutions to meet the needs of communities. To do so, we must relinquish power, center communities, and make way for community agency.

To design and implement inclusionary trials, we must identify and remove exclusionary research practices and advance intentional processes to heal communities. To make such shifts, we need to practice reflexivity personally and professionally (70,71). When institutional behavior shifts and we demonstrate for communities our trustworthiness, communities will see the role of science in improving their lives (72). This observation will have the ripple effect of increasing awareness, research participation, trust, and efficacy—thus, enhancing our ability to conduct rigorous inclusionary research that can improve scientific outcomes. We must shift our focus from seeing how funders and scientific researchers benefit above others, to acknowledging how we can leverage our scientific privilege to benefit communities.

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Table 1. Best practices in community engagement that provide benefit to communities.

Engagement Activity	Best Practices	Benefits to Community
Increase Knowledge and Access to Trustworthy Information	• Share information on the purpose of research in easily understandable, culturally informed ways • Share research results, reporting back to the community in a timely fashion and in easily understandable, accessible ways • Remain engaged with communities after the clinical research. Share trial updates—like FDA approval, results from other studies, or adverse events—to strengthen community relationships and build trust • Co-create with community partners and distribute accessible, trusted resources and services about COVID-19 • Be available to respond to questions in easily understandable, accessible ways • Address community members' specific concerns, questions and needs, including information about other health topics	Research volunteers and their families and friends gain knowledge about prevention, diagnosis, and treatment of COVID-19 from trustworthy sources. This can counter misinformation and can benefit current and future generations.
Build Trust in Research	• Acknowledge past research injustices, if relevant, and demonstrate how a clinical trial can be just, ethical, safe, and meaningful for the community. Avoid using "research subject" terminology • Be transparent about the research process, how it protects individuals and how it helps to right the wrongs of past injustices • Engage communities to identify high-priority research as the perceived benefits and value of research may vary across communities informed ways • Engage community members in planning the research	Research volunteers, their families, and friends can learn about the value of science and how they can be protected and respected.
Strengthen Community Access to Resources	• During a trial, provide needed resources—such as information, referral for medical care, preventive strategies, food security, digital access—to volunteers and/or the community • After a clinical trial, successful treatments should be made available to volunteers who received the placebo • After approval, the treatment should be available, affordable, and accessible to volunteers and their community	Research volunteers and their families and friends gain access to diagnostic, therapeutic, preventive resources for volunteers and others.

Build Community Capacity	• Include community members on the research team whenever possible to draw on their lived experiences • Hire community members to help conduct research—developing materials, recruiting participants, and collecting and interpreting data • Nurture and mentor young people in science and healthcare	Collaborating with community members in research can build community capacity, develop future scientific partners and build trust.