The Inequitable Past of Clinical Trials and a Look Towards a Representative Future

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

The history of public health, research, and clinical trials is one filled with the mistreatment and exploitation of underprivileged groups. In more modern history, the prevalent theories of eugenics of the late 19th and early 20th century in the scientific world influenced beliefs, studies, and the treatment of underprivileged groups. Eugenicists believed that all complexities of humanity including socioeconomic status, social behaviors, and complex diseases were derived entirely through heredity. This led to barbaric scientific practices, studies, and experiments on underprivileged groups, most notably seen in Nazi Germany with their policies of "racial cleansing," including the forced sterilization of over 400,000 victims, mainly Jews (National Human Genome Research Institute). Thousands of prisoners were subject to barbaric and often deadly experiments against their wills, leading to the medical professionals standing trial after the war. This trial established the Nuremberg Code, a fundamental and lasting document on medical ethics that outlines legitimate research practices (United State Holocaust Memorial Museum).

Despite further legislation and policies around experiments and clinical trials building upon the Nuremberg Code, one large issue prevails: underrepresentation of underprivileged groups in trials. The participants in clinical trials have traditionally not been representative of our society as a whole, resulting in fewer positive outcomes for certain marginalized groups. One scathing example is in 2015 when black Americans were under-represented in multiple myeloma trials despite suffering from multiple myeloma at twice the rate as white Americans (Chen & Wong, 2018). This paper will include a review of the current challenges and future opportunities to increase minority representation in clinical trials through a utilization of the ethics of care STS Framework.

Clinical Trials Background

Clinical trials are a crucial stage during the process of drug development, which usually takes around 10 to 15 years. According to Chaudhari et al. (2020) in a paper published by the Indian Society for Clinical Research in their quarterly edition of Perspectives in Clinical Research, recruitment and retention are often the two largest delays in the process. They identify recruitment in a clinical trial as including the following steps:

1. Identifying or sourcing potential participants who may be eligible
2. Discussing all aspects of the trial with them, ensuring comprehension and voluntariness, and subsequently obtaining informed consent for participation
3. Conducting a physical examination and screening procedures as mentioned in the protocol
4. Enrolling the participant based on the eligibility criteria.

Effective recruitment in clinical trials is often tedious, expensive, and difficult to accomplish. It is no surprise, then, that diversity finds itself ignored far too often in recruitment for trials. In the world of clinical trials, the lack of diverse subject groups leads to adverse effects for both privileged and underprivileged groups. According to Bonevski et al. (2014) in a peer-reviewed systematic review of over 100 related studies, these adverse effects include threats to external validity of the study, the inability to accurately extrapolate findings to a broad population, the health benefits of trials being reserved for privileged groups, negative and unforeseen side effects for sub-groups of the population, and a missed opportunity to identify and understand why certain groups face a disproportionately higher burden of certain illnesses.

Criteria for minority representation in clinical trials already exists but is not being followed. The NIH Revitalization Act of 1993 requires that federally funded trials prioritize the inclusion

of women and minorities and that this demographic information be included in publications for accountability; despite this, less than 2% of over 10,000 cancer trials examined after the passing of the NIH Revitalization Act met the stated criteria, with less than 5% even reporting inclusion of minorities (Oh et al., 2015). Clearly, the inclusivity of clinical trials is not being prioritized by trial organizers, and the NIH is not holding them accountable. Some might argue that since clinical trial participation is voluntary, the negative impacts seen in underprivileged groups for a lack of participation is their own fault. This argument fails to integrate essential context around this issue and does not afford these groups an appropriate ethics of care.

Ethics of Care

First developed by Carol Gilligan in 1977 and later elaborated on by Taylor (2020), the framework of ethics of care defines a system, or society, as a network of relationships of caring for one another. This framework provides a basis for how individuals might act seemingly irrationally, bounded by responsibility to others instead of traditional incentives. Taylor (2020) writes that less-visible groups are more likely to be those who act outside of traditional, expected norms. In the context of this topic, minority groups not responding to trial recruitment is a perfect example of this behavior within the ethics of care framework. A greater ethics of care is owed to these people in understanding the context as to why trial participation is low, including what actors are involved and what barriers might exist to voluntary participation.

The COVID-19 pandemic brought upon us a number of government-approved technologies for infection tracking purposes, such as COVIDWISE, utilized by the Government of Virginia. These government-sponsored technologies gathered COVID-19 test data and location data from users to warn them about COVID-19 exposure risks. Taylor (2020) argues that through an ethics of care framework, it would be preferable to devote more resources to

prevention than tracking and to focus those prevention resources for more at-risk communities. The tracking system, as a whole, relies on data from positive COVID tests and the reporting of these positives through a smartphone app. This leaves lower class individuals "invisible" in the data, as they don't test regularly and might not be willing or able to report a positive test result. The identification of this invisible portion of the data is an example of the application of ethics of care; making decisions based on COVID-19 tracking data was common during the pandemic, but a further application of ethics of care would create the need to apply context to the data, identify the invisible populations, and dedicate resources towards those at-risk individuals and groups.

When analyzing the underrepresentation of minority groups in clinical trials, trial organizers need to offer a higher ethics of care to understand the barriers to participation and how to ease them for underprivileged groups. Applying an ethics of care framework also sheds light on a large issue with trial recruitment: organizers trying to recruit populations, not individuals. Taylor (2020) writes, "An ethics of care demands that science-based policy reorient regularly from the notion of the majority to that of the collective. Seeing people and groups rather than populations offers more possibilities for taking particular vulnerabilities into account" (p.5). Trial organizers might focus solely on recruiting a quota for minority populations and ignore the people behind the numbers. This recruitment approach is one of many factors leading to the barrier of distrust between minority groups and the medical world, especially in clinical trials.

Barriers

Bonevski et al. (2014), in a review of 58 "recruitment" studies that met the criteria for selection, identified many barriers for minority recruitment. Commonly cited is a lack of trust in the research team, fear of authority, perceived harms of research, and fears of mistreatment and

exploitation. It should be no surprise that minority groups with a history of abuse in medical research now fear medical research and authority in general. For black Americans, the largest example of this mistreatment is the Syphilis Study of Tuskegee (SST). According to the CDC, the US Public Health Service sponsored a study evaluating untreated syphilis in hundreds of black men in 1932 which continued to 1972, despite penicillin becoming a reliable syphilis treatment in the mid-1940s (The Tuskegee Timeline, 2021). This is one of many instances of abuse and dishonesty exerted by medical professionals on underprivileged communities. While ~72% of black Americans sampled by Mays et al. (2012) were unaware of the SST, it is theorized that what is symbolically represented by the SST is a larger barrier than the SST itself. As demanded by the ethics of care framework, this story of abuse and others like it must be included in the discussion of underrepresentation of minority groups in trials.

In addition to recruitment, trial organizers also struggle greatly with retention. Bonevski et al. (2014) identified practical barriers such as transportation, lack of child care, and lack of leave from work as major obstacles for minority group retention, especially for those of a lower socioeconomic background. The ethics of care framework implies that different groups and people necessitate different treatment and recruitment/retention methods. Lower class participants might need shuttle services, remote-based trials (as opposed to clinic-based), flexible trial time options to balance work shifts, day-care on site for participant's children, etc. Difficulty maintaining contact and the participants forgetting to return for follow-up were also cited as barriers. One strategy outlined for addressing this barrier is clearly highlighting the benefits of research, both at the beginning and during follow-up contact. Novel health benefits will bring people into the door and increase retention if advertised well. This was seen at the extreme with the AIDS Coalition to Unleash Power (ACT UP), when a life-or-death situation

created a large rallying cry for access to experimental drugs. Nurith Aizenman (2019), long-time writer about national health policy for the Washington Post and NPR, tells the empowering story of AIDS patients' response to the FDA not providing experimental drug access to AIDS patients. Following direct protests, the FDA agreed to change their policy regarding access to trial drugs moving forward, and the NIH and pharmaceutical companies began researching AIDS treatments in parallel with research of a cure. It shouldn't take friends and family dying or large-scale protests for it to be known that experimental drugs are out there and might help with a wide variety of issues. Trial organizers can ease the communication barrier to trial recruitment and retention through better information campaigns regarding the potential health benefits of their studies, especially for marginalized groups.

Solutions

Oh et al. (2015), in a review of the lingering impact of the NIH Revitalization Act of 1993 supported in part by NIH grants, identified similar barriers as Bonevski et al. (2014) to minority group participation and some potential solutions to improve the situation. First and foremost, a lack of diversity in the research community directly leads to a lack of diversity in trial participants. Many participants are more likely to be involved if the research staff, either in recruiting or in the experiment itself, are reflective of their own culture and able to be communicate in the participant's native language. There is a distinct lack of diversity in NIH Principal Investigators, those in charge of conducting biomedical or behavioral research within the NIH Intramural Research Program. Less than 2% of them are black, 3.4% are Latino, 0.4% are American Indian and Alaska Natives, and 1.2% are Native Hawaiian and other Pacific Islanders (Oh et al., 2015). All of these groups are underrepresented when compared to their presence in the United States. Additionally, the NIH is less likely to award grants for non-white

applicants than white applicants (6.5% lower in 1985 and 4% lower in 2013). The NIH has also acknowledged that minority investigators receive lower scores from peer review; this is partly due to only 10.3% of NIH study section reviewers in 2013 belonging to underrepresented minority groups. The NIH should not hire diverse people for diversity's sake, but they should strive to empower historically marginalized populations both within the organization and on the outside looking in.

As discussed earlier, some of the largest barriers to clinical trial recruitment and retention, especially for participants on a lower socioeconomic status, are practical barriers like time constraints and a lack of transportation options. Stewart et al. (2022) conducted an investigation comparing diversity within a typical clinic-based trial and within remote-based trials with modern recruitment methods. For the remote studies, online advertising was utilized for recruitment in addition to clinician referral and self-referral through the study website. Participation in the clinical trial was reserved only for those referred by a clinician. All of the studies had a clinical center in Seattle, Washington, but the remote trials had collaborating sites in many other cities. It was found that in comparable randomized clinical COVID-19 trials, the remote-based study population on average was 11 years younger and 6% more female than clinic-based study populations. The white population was also around 50% for the remote-based trials, which is more reflective of American society than the 85% white study population found in the clinic-based trial. While the sample size in the review of Stewart et al. (2022) is small, the results are very promising and provide a path forward for increasing minority recruitment and retention through remote-based trial options in marginalized communities.

The final recommendation by Bonevski et al. (2014) is that there is not one single solution to addressing the barriers that exist for minority group participation in clinical trials. All

forms of medical research should employ strategies to increase representation, but strategies will vary based on the research population, study types, and research questions. The recommendations of this paper unknowingly employ an ethics of care framework such that a comprehensive, coordinated, multi-pronged approach is recommended to address the numerous and unique barriers and challenges that exist for marginalized groups. The number one recommendation given is to adopt a long-term view of the relationship between socially disadvantaged groups and clinical research; context and history must be considered, and new bridges of trust must be built within communities. The second recommendation given is that more resources, including personnel and resource costs, are required to increase representation in trials. Establishing research centers or collaboration centers within socially disadvantaged communities, providing remote trial telemedicine and supplies, ensuring a bilingual research staff, developing unique strategies for representation fitting for the unique circumstances of each trial, and providing flexibility in location and time are all proven strategies for improving representation, but all demand larger investments in studies. Study organizers should not shy from these costs, and funding organizations should be active and willing to fund higher costs for diversity's sake.

Conclusion

Only 80 years removed from the scientific atrocities committed by Nazi Germany and the establishment of the Nuremberg Code, and only 50 years removed from the conclusion of the Syphilis Study of Tuskegee, it is unrealistic to expect that the clinical trial situation now should be perfect. With these scathing examples in recent memory, we should be fighting more than ever to improve racial, socioeconomic, and geographical representation in clinical trials. Diversity far too often finds itself underprioritized in medical research, largely due to the costs

and difficulties involved. Underrepresentation is not an issue that policy alone will fix, as illustrated by the ineffectiveness of the NIH Revitalization Act of 1993. Applying an ethics of care framework brings to light the need to rebuild bonds of trust between underprivileged communities and medical professionals. Further context needs to be considered by trial organizers and sponsors to understand and empathize with marginalized communities and their history of abuse within medical research. This research paper has outlined a number of diversity issues, barriers to participation, and solutions for easing these barriers. For those who might believe that an increase in funding and attention for diversity in clinical trials is unnecessary and only serves the marginalized groups in question, it needs to be stressed that a more diverse study body is beneficial for all stakeholders involved. Studies with a more representative study body allow for more accurate generalizations and more robust findings, both for privileged and unprivileged groups alike. An improvement in clinical trial diversity requires an increase in attention and resource allocation which should be embraced by all for the advancement of scientific innovation and the betterment of humanity.

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