Ensuring Diversity in COVID-19 Vaccine Registration Trials

While much more information needs to be learned about COVID-19, it has become clear that relatively poorer outcomes and the risk of mortality in the US population is alarmingly 2.5 times greater in the black population, and 1.2 times greater in Hispanics, than in whites. Some of the reasons advanced for this worrisome discrepancy are higher prevalence of comorbid illnesses such as diabetes, obesity and cardiovascular disease, restricted access to healthcare, relatively crowded housing conditions, and riskier essential occupations which often demand violating social distancing guidelines[1]. Minority healthcare workers are more likely to report using inadequate or reused protective gear, and nearly twice as likely as white counterparts to test positive for the coronavirus. Recognising the role that socioeconomic status plays in COVID-19 outcomes, the income gap may partially explain the increase in deaths seen in lower-income groups but does not explicate the relatively higher death rates of black people and Hispanics in higher income groups. To date there are no obvious pathophysiological explanations behind the ethnic/racial/minority mortality differences observed with COVID-19.

The poorer outcomes seen in underserved communities have all been in response to therapeutic treatments. However, with several COVID-19 vaccine trials beginning to enter Phase III testing in the US, UK and China recently, it is important to understand if comparable inferior outcomes will be evidenced in minority populations' response to COVID-19 vaccine candidates. To determine this, clinical triallists will need to ensure that the data generated in these vaccine registration trials are statistically robust and generalisable across ethnic populations, particularly blacks and Hispanics, but also Asians and indigenous people.

One might assume that in large vaccine trials enrolling greater than 20-30,000 subjects, ethnically diverse underserved populations of various ages and health concerns would be adequately represented, permitting firm statistical conclusions regarding efficacy and safety. However, the number of potential variables that may impact these trials is so numerous that important findings may be obscured or misrepresentative, despite such large enrolment numbers.

Additionally, in terms of vaccine adoption, individuals from black and Hispanic US communities are historically less likely to receive yearly influenza vaccinations than their white counterparts irrespective of age[2], pointing to the need to ensure adequate representation of all ethnicities in vaccine trials. We know that, for the influenza virus, there are significant variations in genetic factors in vaccine response with one important human gene having 14 different forms that vary greatly between blacks, Asians, and whites. As the different polymorphic forms of the antibody produced bind to different targets on the viral surface, there could be potentially significant variation in vaccine effectiveness[3]. To the contrary, with the H1N1 influenza virus, the black population had significantly greater antibody titres compared to whites[4]. Nonetheless there were higher rates of hospitalisation seen in this ethnic group during the 2009 H1N1 influenza season, which the Centers for Disease Control and Prevention (CDC) suggested may be due to greater preponderance of susceptible underlying conditions, such as asthma and diabetes[5]. These examples (albeit for a different viral class than COVID-19) serve to illustrate that outcomes for individual minority groups cannot be predicted in advance without collecting important variables from specific populations when testing new vaccine candidates.

Therefore, a proactive enrolment strategy is urgently needed to ensure adequate ethnic representation in COVID-19 vaccine trials that is sufficiently representative of a country or region, so that statistical robustness can be confidently applied to both efficacy and risks of a novel vaccine that are pertinent to specific minority groups. If risks are potentially related to ethnicity, then calculations will also need to specify the number of subjects per patient group needed to confidently identify less common adverse events according to a pre-determined threshold. Given the large subject numbers required for enrolment, it should be relatively easy to identify common adverse events, but rare events which may be related to ethnicity and other independent factors may require increased numbers within each population in order to identify risks which occur at less than a 1% incidence at a high degree of confidence.

A proactive approach to recruitment can best be accomplished by having a wide national and global reach, with the understanding of important cultural and ethnic factors in the various countries included in the trial, as well as the ability to target desired demographic variables by assisting sites with links to social media, community organisations/foundations and clinics such as those specialising in comorbid illness such as diabetes and cardiovascular disease. It will be necessary to continuously track incoming demographic data and efficiently adjust recruitment strategies in order to meet the necessary demographic targets per subject cohort for enrolment.

Regulatory Guidance on Diversity in Clinical Trials

Although the number of countries submitting clinical trial data to the FDA has doubled over the past two decades, the proportion of white participants in clinical trials has actually declined, from 92% to 86%. As a result, several measures, acts and guidances have been put in place to ensure more diversity and inclusion in the clinical trial process. One of the most noteworthy of these is the FDA guidance posted in June 2019 concerning "Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs" which serves as a helpful general starting guide to ensure ethnic diversity in clinical trials[6]. This guidance provides wide-ranging recommendations including broadening eligibility criteria to increase diversity in enrolment, making trial participation less burdensome for participants, and adopting enrolment and

retention practices that enhance inclusiveness of underrepresented minority communities. Presciently, the FDA recommended that researchers reduce the frequency of study visits to those needed to appropriately monitor safety and efficacy, and to consider flexibility in visit windows, as well as the use of electronic communication devices (e.g., telephone/mobile telephone, secured electronic mail, social media platforms) or mobile technology tools that can be used to replace site visits and provide investigators with real-time data – all of which have become important tools during the COVID-19 pandemic. An obvious criticism is that these electronic platforms and devices may not be as readily available to lower-income subjects and these ostensibly helpful actions may actually result in less inclusion of underrepresented minority subjects overall, unless this equipment and internet infrastructure is being supplied by the sponsor or site; a practice that is increasingly less common in the current BYOD (bring your own device) research environment encouraged by many electronic patient-reported outcome (ePRO) vendors.

Of note, FDA guidance also recommends that during the recruitment process potential subjects should be made aware of financial reimbursements for expenses associated with costs incurred by participation in clinical trials related to travel and lodging expenses. Importantly, the FDA does not consider reimbursement for reasonable travel expenses to and from the clinical trial site and associated costs such as parking and lodging as characterizing undue influence[7]. Appropriate, simple and rapid reimbursement may be especially beneficial to low-income subjects, and numerous patient support vendors provide such financial services. Specifically, many of these vendors support the use of a "patient reimbursement card" which can be immediately updated with payments from the site once a procedure or site visit is completed.

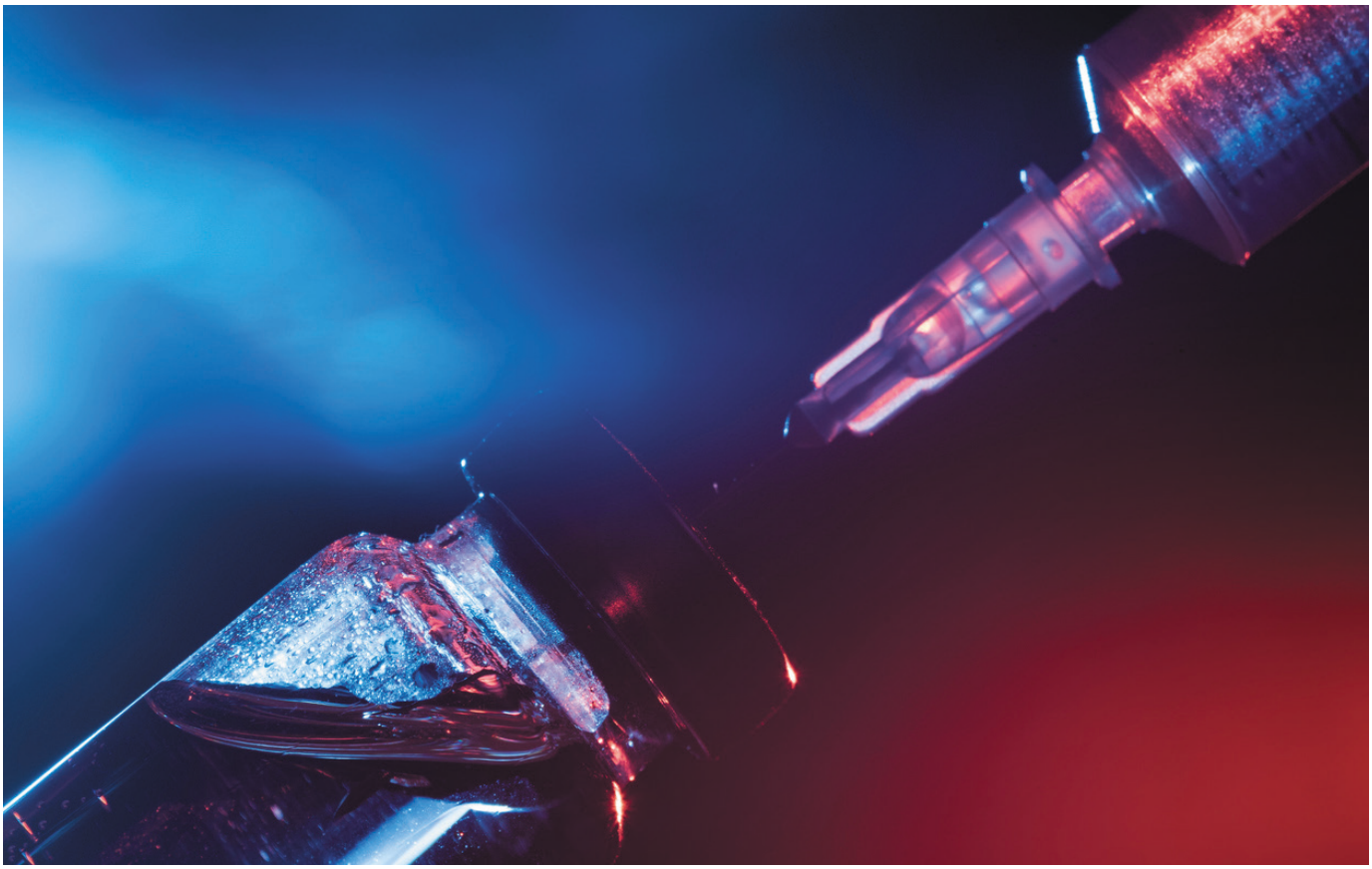
The FDA guidance also encourages researchers to use enrolment and retention practices to enhance inclusiveness. As such, researchers are encouraged to work directly with communities to address subjects' needs and endeavour to involve subjects, advocates, and caregivers in the design of study protocols as much as possible as they are more likely to provide valuable insights into challenges and burdens as well as risks/benefits that may be unknown to site staff. Community engagement and the use of medical advocates/liaisons also known as "patient navigators" has been very successful in specific underserved and minority community recruitment efforts. Explicitly, guidance recommends that sites hold recruitment events often that are easily accessible during evening and weekend hours and having these in trusted community locations as a means of connecting with diverse subject groups.

Although these recommendations are generally quite useful and serve as a good starting-point, this guidance is intended mostly for enrolment in treatment studies and are not specific to vaccine studies, and does not go nearly far enough in addressing specific barriers to enrolment of diverse populations and how these can be successfully overcome in vaccine studies. In regards to vaccine studies there is much more work to be done, and steps to be taken in providing information and educating underserved minority groups about clinical research and the development journey of products may be helpful in increasing awareness. Unfortunately, guidelines from the FDA for COVID-19 vaccines FDA "encourages" enrolment of racial and ethnic minorities but do not require it for approval[8].

Specific Barriers to Enrolment in Vaccine Studies

There have been several efforts to identify the most important barriers to enrolling diverse populations in clinical trials. Based on literature review and evaluation, as well as vital input from key stakeholders, including minority subjects and referring physicians, Clark *et al.*[9] have suggested the following three broadly-defined categories of critical barriers to minority participation in clinical trials: (1) mistrust, including lack of information about and comfort with the research process; (2) logistical barriers such as time and resource constraints; and (3) limited clinical trial awareness.

Researchers tend to spend much of their efforts focusing on solutions related to logistical considerations, as these are most easily addressed and seem to resonate with subjects, including providing transportation, flexible hours for subjects, appropriate compensation, and mobile technology support such as an app for subjects and



mobile phones for those who do not have one. Addressing subjects' logistical and financial concerns also permits more patient-centricity in trials and may not only increase the likelihood of participation but also may increase satisfaction and improve the overall experience of minority subjects[9].

However, although important for recruitment of minority subjects across virtually all clinical trials sites, it may not be fully appreciated that the foremost issue for most minority subjects seems to be "trust" – an issue which appears to be amplified for trials involving vaccines. Despite the fact that specific minority groups stand to benefit enormously from the development of a safe and effective COVID-19 vaccine, some groups from underserved communities remain distinctively distrustful of the medical establishment. This distrust is likely based on current disparities in healthcare access as well as past transgressions, such as the Tuskegee syphilis experiment, which was so profoundly disturbing and predominant that the lack of trust in the research process is often referred to as the "Tuskegee effect". This effect is echoed in a recent news poll suggesting only 32 per cent of black adults said they would definitely get a vaccine, compared with 45 per cent of whites and Hispanics[10]. Of note, annual reports from the CDC on vaccination rates for diseases like influenza, pneumococcal pneumonia, HPV and herpes zoster commonly confirm that racial and ethnic vaccination differences persist for all vaccinations, with generally lower coverage for most vaccinations among black, Hispanic, and Asian adults compared with white adults.

Furthermore, notwithstanding the absence of an actual approved vaccine for COVID-19, there is a very robust and organised multinational "antivax" movement which has been extremely vocal in regard to unfounded assertions of disproportionate harm to minority and underserved groups. Confounding this issue, several national public health groups have publicly considered offering some of the first approved vaccine doses of the COVID-19 vaccine to the most vulnerable groups, including the elderly, healthcare workers and those at greatest risk of harm, as well as diverse populations such as blacks, Hispanics and indigenous peoples, as part of a larger public health plan. However sincere these motives may be (reflecting the desire to provide the vaccine to those most in need), they have been called into question with criticisms of underserved minority populations serving as "guinea pigs" for subsequent majority populations who would be dosed once more information on safety is known.

In order to overcome issues such as these, it will be important to build trust within various minority groups by partnering with multicultural professional associations and by utilizing patient navigators on a local level whenever possible. In a recent survey, Lavinia et al. reported that 44% of the site respondents indicated that the use of patient navigators was one of the most effective methods of improving recruitment of underserved minority participants into clinical trials, and particularly in assisting with clinical trial education[11]. Communication about clinical trial opportunities through postings on various websites and through written materials translated into numerous languages were also reported to be effective, as was the use of financial incentives including the use of prompt travel reimbursement and monetary incentives. As noted, technology is also helping to drive better research and development of treatments and ensuring that historically excluded minority communities are given the same access to medical advancements and trials[12]. One unanticipated outcome of the COVID-19 pandemic is that many clinical trials are finally utilising technology to their advantage, whether replacing or supplementing traditional clinic visits with virtual visits which can also aid recruitment efforts given the reluctance of some patient groups to come into site/hospital settings. Furthermore, tablets/devices can be used outside the traditional bounds of a trial to gather important information on symptoms that might be used to more clearly identify patient subgroups that respond to vaccine candidates as well as on outcome measures that can reliably assess the longer-term efficacy and safety of vaccines.

Summary

Increasing clinical trial participation in COVID-19 vaccine registration studies among minority and underserved populations will require a paradigm shift in researchers' approaches to and conduct of clinical trials, and importantly, in how researchers engage their communities. Large-scale registration COVID-19 vaccine trials can only provide meaningful and generalisable data regarding a specific subgroup's success and safety rates if diverse communities are recruited, and if all important information is fastidiously collected, including at a minimum, age, gender, ethnicity/race, socioeconomic status, residential/occupational status and comorbid medical conditions. Any significant lack of diversity in the clinical trial process can result in efficacy and safety outcomes that may be flawed and distorted; and when diverse populations are knowingly excluded from vaccine trials there is a real risk of making assumptions about drug safety and effectiveness that may not be accurate at all[12]. There are also pragmatic reasons for minority recruitment in regard to vaccine trials which demand that subjects eventually be exposed to SARS-CoV-2 in order to determine efficacy as this exposure has been shown to be more pervasive in underserved minority communities. Given the myriad scientific, ethical and practical reasons, it is imperative that researchers attempt to fill the breach in trial participation among minority and underserved minority populations for COVID-19 vaccines by using some of the tools suggested above and frankly, by any and all means possible.

REFERENCES

1. Center for Disease Control and Prevention (CDC) website report, July 24, 2020. Provisional Death Counts for Coronavirus Disease 2019 (COVID-19). Healthcare Disparities: Race and Hispanic Origin. https://www.cdc.gov/nchs/nvss/vsrr/covid19/health_disparities.htm
2. Egede LE and Zheng D; Racial/Ethnic Differences in Adult Vaccination among Individuals with Diabetes. Am J Public Health 93(2):324-329, 2003
3. Avnir Y et al.; IGHV1-69 Polymorphism modulates Anti-Influenza Antibody Repertoires, correlates with IGNV Utilization Shifts and varies by Ethnicity. Science Reports 6:20842, 2016.
4. Kurupati R et al.; Race-Related Differences in Antibody Responses to the Inactivated Influenza Vaccine are linked to Distinct Pre-Vaccination Gene Expression Profiles in Blood. Oncotarget online, oncotarget 11704, 2016.
5. CDC website report 2009 H1N1 and Seasonal Flu and African American Communities: Questions and Answers. https://www.cdc.gov/h1n1flu/african_americans_qa.htm
6. Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Design https://www.fda.gov/media/127712/download
7. Payment and Reimbursement to Research Subjects — Information Sheet (January 2019), available at https://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm
8. Covid-19 Vaccine Trials Have a Problem: Minority Groups Don't Trust Them available at: https://www-wsj-com.cdn.ampproject.org/c/s/www.wsj.com/amp/articles/covid-19-vaccine-trials-have-a-problem-minority-groups-dont-trust-them-11596619802
9. Clark LT, Watkins L, Piña IL, Elmer M, Akinboboye O, Gorham M, Jamerson B, McCullough C, Pierre C, Polis AB, Puckrein G and Regnante JM; Increasing Diversity in Clinical Trials: Overcoming Critical Barriers. Current Problems in Cardiology, 08 Nov 2018, 44(5):148-172.
10. Goldstein A and Clement S; June 2, 2020. 7 in 10 Americans would be likely to get a coronavirus vaccine, Post-ABC poll finds https://www.washingtonpost.com/health/7-in-10-americans-would-be-likely-to-get-a-coronavirus-vaccine-a-post-abc-poll-finds/2020/06/01/4d1f8f68-a429-11ea-bb20-ebf0921f3bbd_story.html
11. Lavinia D and Gansauer L; Recruiting and Retaining Minorities in Oncology Clinical Trials: A Nurse Navigator Perspective. Journal of Oncology Navigator and Survivorship. Sept 2018 Vol 9, No 9mber . http://www.jons-online.com/issues/2018/september-2018-vol-9-no-9/1976-recruiting-and-retaining-minorities-in-oncology-clinical-trials-a-nurse-navigator-perspective
12. Hebenstreit C; How Technology Is Helping Increase Diversity In Clinical Trials https://www.forbes.com/sites/forbestechcouncil/2020/06/18/how-technology-is-helping-increase-diversity-in-clinical-trials/#1bf39ca4bf89

Henry J. Riordan

Dr. Riordan is the Chief Development Officer at Worldwide Clinical Trials. He has been involved in the assessment, treatment and investigation of various neuroscience drugs and disorders in both industry and academia for the past 25 years. He has over 120 publications, including co-authoring two books focusing on innovative clinical trials methodology.

Email: henry.riordan@worldwide.com

Drew Matheson

Drew Matheson is the Executive Director of the Immune Mediated Inflammatory Disorders Division and is the Pandemic Response Lead for the COVID-19 Task Force at Worldwide Clinical Trials and as such oversees all ongoing COVID-19 trials. Specialising in project management and statistical support in complex project environments, including a focus on device trials, Drew has worked in clinical research for more than 20 years, leveraging invaluable, fundamental knowledge of the ins and outs of clinical research.

Email: drew.matheson@worldwide.com

Natalia E. Drosopoulou

Dr. Drosopoulou is the Executive Director and Global Franchise Leader at Worldwide Clinical Trials who leads the International Clinical Project Management Team. She received her PhD in biochemistry specialising in developmental neurobiology from King's College of London. With over 18 years in the clinical research industry, her experience spans from small intricate Phase I studies to large global Phase III programmes.

Email: natalia.drosopoulou@worldwide.com

Aman Khera

Aman Khera is Global Head of Regulatory Strategy at Worldwide Clinical Trials. Ms Khera has over 23 years' industry experience in providing global strategic direction in regulatory affairs. She has led a wide variety of regulatory projects providing regulatory strategy and development services for a variety of client sponsor companies in many therapeutic indications. Ms Khera is well versed in developing comprehensive regulatory strategies. Her career is built on helping client sponsor companies achieve their end-to-end regulatory strategies from study submission to commercialisation.

Email: aman.khera@worldwide.com