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Expanding The Tent: Improving Trial Participation Among Under-Represented Patient Populations

New Tufts CSDD Research Creates A Baseline For Change

by Ben Comer

The biopharma industry has struggled to recruit patients into clinical trials that adequately reflect the diverse patient populations they hope to reach with new products. Failure to improve minority subgroup participation now will cost trial sponsors later.

- New Research from the Tufts Center for the Study of Drug Development reveals the extent to which minority groups are absent from clinical trials supporting new drug and biologic approvals.
- Additional tools are emerging to help sponsors effectively recruit and enroll underrepresented patient populations in clinical trials.
- Patient engagement approaches should be tailored to reflect the needs of specific patients and communities.

The strength and authority of science in society, such as it is, relies on a commonly held belief that scientific findings are objective and impervious to the biases of its practitioners. Scientific facts – including the way human bodies respond to medical interventions – must be recognized and trusted as facts, until new studies and experiments come along to update the old facts or replace them. Identifying and controlling for variables during a clinical study is a key principle of the scientific enterprise, one that distinguishes rigorous and actionable conclusions from studies that distort reality, lead to poor policy decisions, or worse.

All studies have limitations, whether they are acknowledged or not: human biology, including the function of roughly 20% of proteins in the body, for example, remains a mystery. The mechanism of action for many drugs used to treat central nervous disorders, for another example, are not well understood. And yet, scientists and clinicians have uncovered important distinctions between individuals across ethnicity, gender and age groups, and how they respond differently to specific medications. In the race to bring new treatments and vaccines to bear on COVID-19 infections across the globe - and across ethnic groups - trial sponsors should make sure these distinctions are sufficiently elucidated, and communicated to physicians.

What is surprising – or perhaps not, from a historical perspective – is that in 2020, minority groups remain woefully underrepresented in FDA-regulated clinical trials. Of the six new molecular entities (NMEs) approved by the FDA between 1 January 2020 and 26 February 2020, five did not have enough non-white participants in supporting clinical trials to determine differences in response or side effects, according to the FDA's Drug Trial Snapshots.

Numerous studies have shown that differences often do exist, beyond well-known examples of blood thinners or hypertensive agents. Of the 167 NMEs approved between 2008 and 2013, 35 (roughly one-fifth) contained product labeling about race or ethnic differences in pharmacokinetics, safety, efficacy or pharmacogenetics, according to research cited by the Office of Minority Health in a 2016 presentation to Congress.

FDA's Drug Trial Snapshots

Section 907 of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) required the FDA to report on clinical trial diversity according to sex, age and race/ethnicity. The Drug Trials Snapshot program – which includes consumer-friendly information on drug uses, safety information, clinical trial participants and differences in sex, age and race/ethnicity for newly approved NMEs and original biologics – was established in 2014. The stated goal of the program is to make demographic information about participants in pivotal clinical trials more transparent. As of 12 March 2020, there were 243 products covered in Snapshots.

Baseline For Improvement

Despite years of FDA effort and goading to improve minority inclusion rates, obstacles remain. New research from the Tufts Center for the Study of Drug Development (CSDD), led by Ken Getz, professor and deputy director, provides a deep analysis of participant diversity – or lack thereof – in clinical trials supporting new drug approvals between 2007 and 2017. The findings cast the issue in stark relief. "It's the first study that I'm aware of that actually quantifies the magnitude of disparities and underrepresentation in clinical trials across nearly all therapeutic areas," said Getz. "Evidence supporting efficacy and safety of new therapy is not definitive evidence when we don't have representation of the full community of patients who are going to receive that treatment."

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The problem with the FDA's Drug Trial Snapshots program, said Getz, is that it "doesn't give us any information about disease prevalence, and it tells us nothing about whether the demographic distribution, given individual disease prevalence variation, is even representative." The results of the Tufts study, titled *Assessing Participant Disparities in Clinical Trials Supporting New Drugs and Biologics Approved between 2007 and 2017* and supported by a grant from Merck & Co., reveal "data showing substantial underrepresentation of black participants - and to a lesser extent Hispanic participants — in clinical trials" during the 10-year period, said Getz.

The objectives of the CSDD study, which was shared with *In Vivo*, are threefold:

- to assess the availability and disclosure of participant demographic subgroup data provided by pharmaceutical and biotechnology companies to promote greater transparency and accuracy in future assessments of participant diversity;

- to rigorously gather data to inform a baseline assessment of the magnitude of participant demographic subgroup disparities in clinical trials of new drug approvals and ultimately identify opportunities to improve minority underrepresentation and access to investigational treatments; and

- to establish and convey an approach that the FDA – and others in the public and private sector – can apply and adapt to improve the value of the Drug Trial Snapshot program and other disclosure initiatives informing the general public and stakeholders in the clinical research enterprise.

To understand the level of subgroup underrepresentation in trials, the CSDD team compared trial participant demographic data supporting new drugs and biologics during the 10-year period with corresponding disease prevalence rates, and when that was not available, to US census data. For each approved product, CSDD developed a "disparity percentage" representing the difference between the actual number of trial participants by subgroup, and the predicted, or expected, number of participants by subgroup based on prevalence or US census data during the year of the drug approval. That number was then divided by the predicted number to get the disparity percentage (*see exhibit 1*).

Exhibit 1

	Female	Male	White	Black	Asian	Hispanic / Latino	Other
Total participants	469,919	532,628	552,868	40,265	75,134	44,732	19,782
Distribution of Total Participants	46.9%	53.1%	75.4%	5.5%	10.3%	6.1%	2.7%
Predicted Level of Participation (based on census and disease prevalence)	506,734	490,793	508,468	86,694	34,402	57,839	54,356
Predicted Distribution	50.8%	49.2%	68.5%	11.7%	4.6%	7.8%	7.3%
Difference	-36,815	+41,835	+44,400	-46,429	+40,732	-13,107	-34,574
Disparity Percentage*	**-7.3%**	**+8.5%**	**+8.7%**	**-53.5%**	**+118%**	**-22.7%**	**-63.6%**

SOURCE: TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

The highest overall levels of underrepresentation, according to the data, were among black/African descent (-53.5%), Hispanic/Latino (-22.7%) and "other" (63.6%) participant subgroups; the "other" category includes Native American, Native Alaskan, and Hawai'ian or Pacific Islander participants. Overrepresentation among Asian participants in certain therapeutic areas may be due in part to market access requirements in key geographies including Japan and China, a reflection of the global nature of clinical trials.

Data completeness associated with approved products is another concern; reporting participant subgroup information in FDA-regulated drug development is optional, according to the CSDD study. On top of that, subgroup participation itself is not required, either. "The FDA does not

have the regulatory or statutory authority to require that [trial] sponsors include demographic subgroups as participants in their clinical trials," said Lola Fashoyin-Aje, Division of Oncology 3 acting deputy director at the FDA's Office of Oncologic Diseases, during an American Association for Cancer Research workshop held in Washington DC, on 13 February. "FDA can't legally go after sponsors who do not adhere to [FDA proposed] standards," she said.

Interestingly, minority subgroups were well represented in oncology trials between 2007 and 2017, with one glaring exception: Hispanic or Latino participants were markedly underrepresented, despite positive disparity percentage scores among all other races and ethnicities, according to the CSDD study (*see Exhibit 2*). Black participants, or participants of African descent, were underrepresented in roughly two-thirds (68.8%) of the therapeutic areas for which all new drugs and biologics were approved during the 10-year period. Hispanic or Latino patients were similarly underrepresented in 64.3% of all therapeutic areas. Women were notably underrepresented in both immunology and endocrinology therapeutic areas, as well.

Exhibit 2

Figures reflect the percent of drugs within a T.A. which had a disparity of greater than -20%*	**Female**	**Male**	**White**	**Black**	**Asian**	**Hispanic / Latino**	**Other**
Oncology	26.4%	27.9%	3.7%	65.4%	20.0%	100.0%	30.4%
Neurology	45.8%	0.0%	11.1%	100.0%	66.7%	75.0%	100.0%
Cardiology / Vascular Disease	30.0%	5.0%	0.0%	66.7%	75.0%	60.0%	
Endocrinology	50.0%	0.0%	0.0%	33.3%	0.0%	33.3%	0.0%
Infections and Infectious Disease	0.0%	6.7%	8.3%	83.3%	50.0%	44.4%	0.0%
Dermatology	60.0%	20.0%	0.0%	100.0%		0.0%	
Gastroenterology	0.0%	0.0%					
Pulmonary / Respiratory Disease	40.0%	0.0%	0.0%	100.0%		50.0%	66.7%
Psychiatry	20.0%	0.0%	25.0%	50.0%		100%	

Rheumatology	0.0%	30.0%	0.0%	100.0%	100.0%	100.0%	50.0%
Immunology	85.7%	0.0%	0.0%	100.0%	0.0%	60.0%	100.0%
Ophthalmology	25.0%	25.0%	20.0%	60.0%	0.0%	25.0%	100.0%
Musculoskeletal Disease	50.0%	50.0%	0.0%	100.0%			
Hematology	0.0%	0.0%					
Urology	60.0%	40.0%	0.0%	100.0%			
Nephrology	0.0%	0.0%	0.0%	50.0%	50.0%	100.0%	0.0%
Hepatology	0.0%	100%					
OB/GYN	0.0%		0.0%	0.0%		100.0%	

*DISPARITY PERCENTAGE IS THE 'DIFFERENCE' DIVIDED BY PREDICTED LEVEL. SHADED CELLS INDICATE WHERE DATA IS NOT AVAILABLE.
SOURCE: TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

Further Studies Draw Similar Conclusions

A collaboration formed in 2018 between RTI International, a non-profit research institute based In Research Triangle, North Carolina, and Project Data Sphere, an open-access research platform providing de-identified patient-level data from oncology clinical trials, is linking individuals in the national Medical Expenditure Panel Survey (MEPS) with trial data housed in Project Data Sphere. The intent of this project is to understand how representative cancer trial patients were with similar cancer patients in the general population. The linked results, which include data on sociodemographic and health-related characteristics, offers new insights into health disparities research. Among many findings in the initial linkages, researchers found that a cancer patient's likelihood of survival was associated with their insurance coverage status, their status as a smoker, their health preferences, and the amount of services received during outpatient visits with a physician. Lung cancer patients enrolled in clinical trials were more likely to be white, married and current smokers compared with similar patients in the MEPs database, according to a 2018 study published *Frontiers in Oncology*.

Disparities in the practice of medicine are not limited to clinical trial participation. A widely circulated study published by the *Proceedings of the National Academy of Sciences of the United States of America* in 2016 found that many white, US-born medical students and residents did recognize differences between white and black ethnicities; unfortunately, the differences they recognized were false and racially biased. Examples of "false belief items" presented to students and residents as part of the study included "blacks have denser, stronger bones than whites," "blacks' nerve endings are less sensitive than whites," and "blacks' skin is thicker than whites," among others. Approximately 50% of the medical students and residents participating in the study reported that at least one of the false beliefs was possibly, probably or definitely true, according to the study, and participants agreed with 11.55% of the false beliefs, on average. The study's authors concluded that "many white medical students and residents hold beliefs about biological differences between blacks and whites, many of which are false and fantastical in nature … these beliefs are related to racial bias in pain perception."

Prescribing physicians, regardless of ethnicity, may also lack awareness of – or easy access to – drug information related to minority subgroup safety and efficacy information. A study published last September in *Pharmaceutical Medicine* found that between 2008 and 2012, 96% of new chemical entities supported by large-scale clinical trials and registered in both the EU and Singapore contained safety issues specific to ethnic subgroups in their registration dossiers. However, ethnicity-specific safety information was only present in 48% of European public assessment reports, 32% of the European Union summaries of product characteristics, and 36% of the Singapore package inserts for the same products. As a result, the information is often unknown to prescribers in Europe and Singapore, according to the study authors.

Tools For Improving Trial Diversity

Last June, the FDA released new draft guidance for the biopharma industry on "enhancing the diversity of clinical trial populations," with recommendations including:

- expanded eligibility criteria to better reflect all of the patients likely to use a drug; characterizing drug metabolism early in the clinical process, across patient groups that may metabolize a drug differently;
- making trial participation less burdensome for patients by reducing frequency of clinical visits;
- emphasizing remuneration for travel, lodging and other expenses;
- ensure that trial sites include areas with higher numbers of racial or ethnic minorities;
- use mobile and digital tools, including biometric sensors, to replace site visits and produce

real-time data for investigators; and

- engage with patient advocacy groups on trial designs and protocols, especially in rare disease studies, among other recommendations.

- The guidance also references the importance of public outreach and communication, which can be challenging if the needs and cultural makeup of specific communities are not well understood.

Other groups are also taking steps to improve clinical trial diversity. In the UK, Manchester-based Christie NHS Foundation Trust, a leading cancer center in Europe, partnered with clinical trial recruitment company Innovative Trials to improve black, Asian and local minority ethnic community member participation in cancer studies. Andrew Wardley, consultant medical oncologist at The Christie and project lead for the initiative, said that the partnership "is about building the structures that allow people to make decisions about clinical trials and give them the information in a very supportive way, which is often not as optimal as it might be." (Also see "*Interview: UK Initiative Bids To Boost Access To Cancer Clinical Trials*" - Scrip, 9 Mar, 2020.)

Indeed, traditional marketing and advertising channels may not be an effective way to recruit patients from diverse populations into clinical trials, since they often lack the nuance and educational value needed to adequately explain the benefits and risks of trial enrollment. An increasing number of health systems that conduct trials have begun using patient navigators to help with recruitment efforts. These patient navigators focus on providing high-touch, often in-person engagement with potential trial participants. Large providers of electronic health records systems (EHRs), such as Epic and Cerner, are offering “clinical decision support” based on information housed in the EHR. For example, a patient coming in for a doctor’s appointment can trigger a notice to the physician about available trials matching the patient’s profile. Once identified, a patient navigator “can greet the patient at their point of care, and if that particular patient is appropriate for a trial, they can walk them over to the trial office and introduce them to the personnel there,” said Getz. “This high-touch approach holds a lot of promise.” In rare diseases such as lupus, for example, where the prevalence is higher among minority populations, navigators are moving within church systems and community centers, where people congregate, according to Getz.

Rare Disease Recruitment

Locating and recruiting a diversity of patients into clinical trials for rare diseases can be especially challenging and time consuming, given the small number of patients globally. In addition, the study of genetic variants and their relationship to rare diseases is typically accessed and analyzed through large global data banks, which skew dramatically toward Caucasians of European ancestry, said Arndt Rolfs, CEO of Centogene, a Rostock, Germany-based rare disease company focused on identifying causal gene variants and biomarkers. According to a 2016 study

in *Nature*, of the 2,511 genome-wide association studies and 35 million samples collected in 2016, 81% were collected from individuals of European ancestry. "Researchers rely on these databanks despite an obvious bias, even though it's clear that there's a big difference, just in the genetic layer, if we're comparing the genome in an individual coming from Japan, Mongolia, New Zealand or Germany," for example, said Rolfs.

Centogene, which also markets a range of diagnostics and genetic sequencing services, has compiled its own databank and technology platform comprised of genomic, proteomic and metabolomic data from over one million patients. "Roughly 20% of those patients are from the Middle East, 15% are from Latin America, 15% are from North America, 20-25% are from Europe, and the remaining 20-25% are from Asia, New Zealand and Australia," said Rolfs. The company is also currently enrolling patents in 48 observational, non-interventional clinical studies, according to *Clinicaltrials.gov*, to "get a natural history documented from the individual patient on the one hand, and also to develop new biomarkers," he said.

The databank and technology platform can help partners locate and recruit patients faster, notes Rolfs, citing a collaboration with San Francisco-based Denali Therapeutics announced in October of 2018. Denali is developing treatments for a subtype of Parkinson's disease, based on targeting the LRRK2 gene. "Denali had a developmental plan for the recruitment of 500 patients, and had expected to need five years to identify these 500 patients that demonstrate specific mutations within the LRRK2 gene," said Rolfs. "They contacted us, we entered the information into our databank looking for activity in our network, and we immediately identified 3,500 patients globally. So instead of investing money and time identifying patients over the next five years, we have been able to significantly speed up the recruitment of patients for the clinical program." Through an initial consenting process, Centogene is able to contact the physicians of specific patients directly about trial enrollment opportunities.

Patient Attitudes Toward Trial Participation

When discussing clinical trials and the need to recruit more minority participants, it is inevitable that the Tuskegee syphilis study atrocity, or the fact that Henrietta Lacks' cells were stolen without consent, will be mentioned as a contributing factor for mistrust in black communities. That may be true; however, a new global survey from the Center for Information and Study on Clinical Research Participation (CISCRP), a nonprofit focused on educating the public about clinical research, suggests that members of the black community who decided to participate in a trial were significantly less likely than any other subgroup to hear about the trial from a general practitioner or specialist, suggesting a failure by physicians to educate and provide referrals for black patients. Among black trial participants, 8% learned about a trial from their physician, and 20% learned about a trial from an online government database. By comparison, 16% of participants across all ethnicities learned about a trial from their physicians, and 12% learned about trials from an online government database.

Moving all or part of a clinical trial out of the traditional site and into the home, and using concierge services and technology, holds promise for engaging underserved populations, according to the CISCRP survey. Asked about preferences related to visiting a study site versus collecting data at home, 75% of the total respondents (n=12,451) said collecting all study data themselves, at home, was appealing; 79% said nurses traveling to their homes for all study visits was appealing; and having a mix of home and clinical site visits was appealing to 73% of respondents. Forty percent of black respondents found home visits from a nurse to be “very appealing,” compared with 24% of respondents identifying as Asian. Women were also more likely to find home visits from a nurse, and home data collection “very appealing,” compared to male respondents. Asked about the importance of clinical research in the discovery and development of new medicines, respondents identifying as black, and respondents identifying as white, were more likely to feel that clinical research is “very important” compared to other subgroups.

Educating and engaging patients – across all patient populations – will become increasingly important for drug developers, and for patients themselves. With a raft of gene therapies and other expensive specialty medications filling biopharma pipelines, payers have indicated their intent to limit coverage for patient subgroups when clear safety and efficacy data are not available.