COMMENT

CLAUDIA DAUT/REUTERS

A man waits for treatment at a hospital in Havana, where a drug to treat diabetic foot ulcers was shown to be effective in a clinical trial.

When will clinical trials finally reflect diversity?

An analysis of drug studies shows that most participants are white, even though trials are being done in more countries, reveal **Todd C. Knepper** and **Howard L. McLeod**.

Since the late 1990s, the number of countries contributing to the clinical-trial data used by the US Food and Drug Administration (FDA) to approve drugs has almost doubled (see 'Going global'). Yet this global expansion of study locations has not been accompanied by an equivalent increase in the racial diversity of people enrolled. In 1997, 92% of the participants in these trials were white; in 2014, we found that this figure was still nearly 86%.

A growing body of literature indicates that the effectiveness of a drug, the likelihood of it causing side effects and the nature of those effects can all vary between people of different ancestry[1]. And funders and researchers have repeatedly said that clinical trials should include more participants from ethnic minorities. Indeed, 25 years ago the US National Institutes of Health Revitalization Act called for more people from ethnic minorities to be included in clinical trials.

In our view, drug developers should capitalize on the global expansion of clinical-trial locations to design studies that represent more of the world's population.

PROBING THE DATA

To understand which populations provide the drug safety and efficacy information ▶

used by the FDA, we reviewed the approvals made by the agency at five time points from 1997 to 2014. For each approval, we documented the reported race of the people involved in the clinical trial and the country where the trial was conducted. (All were pivotal efficacy trials, generally the most definitive demonstrations of a medicine's efficacy and safety.) We focused only on the categories 'white', 'black', 'Asian' and 'other', because the reporting for these was uniform across countries. The data for ethnicities, such as Hispanic or non-Hispanic people, were confounded by reporting inconsistencies and were therefore omitted from the analysis.

We focused on treatments for heart disease, cancer and disorders of the central nervous system (CNS); 41% of the drug approvals made over the period 1997 to 2014 were for these common global health problems[2]. We assessed FDA approvals because many countries follow the agency's lead when it comes to their own regulatory decisions.

During the five years we assessed (1997, 2004, 2009, 2012 and 2014), 81 drugs for heart disease, CNS disease and cancer won FDA approval (see Supplementary information) on the basis of clinical trials involving nearly 150,000 people. Twenty-nine countries contributed clinical-trial data in every year evaluated. For eastern Europe, Asia-Pacific, Latin America and the Caribbean, representation increased over the study period (see 'Going global'). We classified regions according to the United Nations Regional Groups.

Over the five time points, the racial make-up of the clinical trials stayed relatively stable (see 'Going global'). The median percentage of African and African American participants per trial ranged from 1.8% to 3.5%. For Asian participants, the range was 0% to 7%; for any group unspecified or not described as white, black or Asian, it was 1.4% to 3.4%. For context, according to the US census, 72.7% of the US population was non-Hispanic white in 1997 and by 2014, this figure was 62.2%. Also, as of 2015, around 75% of the global population lived in Asia or Africa[3]. Of course, our analysis has limitations. The ideal mix of race and ethnicity will vary from country to country; we compared the trial demographics to the US population because we used trial data evaluated by the FDA.

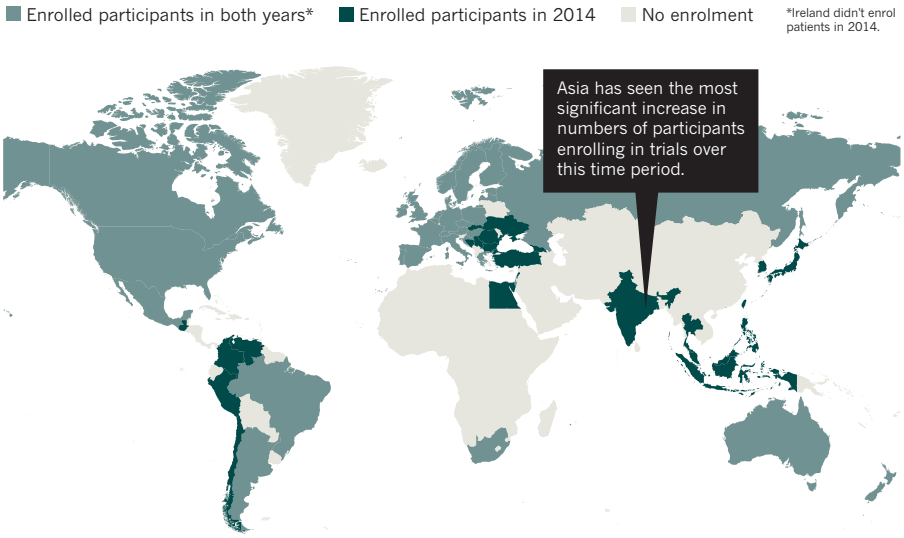
SHIFTING LOCATIONS

There are various possible reasons why the diversity of trial participants is not increasing with the expansion of countries contributing to trial data. It is likely that fewer people are enrolling in the trials or fewer trials are being conducted in those countries that have begun contributing data more recently.

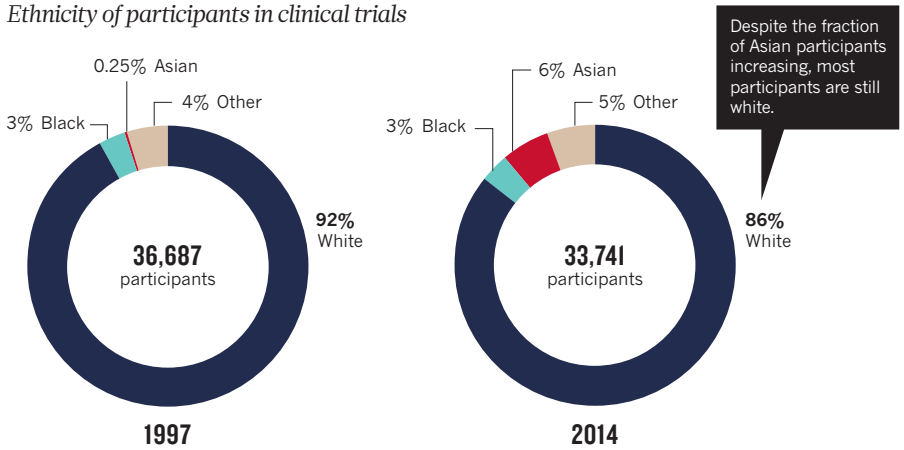
GOING GLOBAL

The number of countries contributing to the clinical-trial data that the US Food and Drug Administration uses to approve drugs almost doubled between 1997 and 2014, from 32 to 57. The racial make-up of the trials was little changed.

Countries contributing to clinical-trial data



Ethnicity of participants in clinical trials



SOURCE: US FOOD AND DRUG ADMINISTRATION

None of the conversations we have had with drug developers suggests that the goal of including greater population diversity in clinical trials is driving the change in where trials are being conducted.

We think that the sharp increase in the number of countries contributing to clinical-trial data (from 32 in 1997 to 57 in 2014) has been driven by two main factors.

The first is a growing shortage of people from developed economies who are eligible for clinical trials. Wealthy countries are better able to adopt new therapies into standard care than are poor countries. So many patients in the United States and western Europe now have access to a variety of medications outside a clinical-trial setting. The scarcity of people with a particular condition who are not already taking medication — 'treatment naive' patients — has prompted drug developers to start recruiting overseas.

The second factor is lower costs. In North America and western Europe, hospitals and other care centres tend to charge drug developers much more for hosting clinical trials than do equivalent institutions in eastern Europe and Asia. Staff expenses also tend to be lower in less-wealthy countries and studies can be completed more quickly.

DRUG EFFICACY

Many studies indicate that the likelihood, nature and severity of side effects from a medication can differ between populations[1].

For example, the antiplatelet drug clopidogrel reduces a person's likelihood of having a heart attack or a stroke after some heart procedures. Genome-wide-association and other studies have revealed that people with certain genetic variants of the *CYP2C19* gene, which encodes an enzyme that activates the drug, might need a different and more expensive therapy[4]. And people of

Asian heritage are three times more likely to produce poorly functioning CYP2C19 enzymes than are people of white heritage[5,6].

Similarly, around 20 years ago, genomic and other studies, predominantly conducted in white populations, identified genetic markers that indicated whether people with cancer would have dangerously low counts of white blood cells after being treated with the autoimmune medicines 6-mercaptopurine (6-MP) or azathioprine[7]. The markers were variants in a gene called *TPMT*. Studies subsequently conducted in Asian and South American patients receiving these drugs identified variants in *NUDT15* as the key predictor of whether the drug is toxic to a person's white blood cells[8,9]. An important patient-safety marker had been missed for nearly two decades owing to a lack of comprehensive genomic testing.

MOVING FORWARD

Various efforts are under way to raise awareness about the importance of population diversity in clinical trials, and to improve the quality of the data that are collected on race and ethnicity (see 'Documenting diversity'). Too much of what we know about population differences in drug responses is anecdotal or stems from observations of a handful of patients. Most clinical trials do not enrol enough patients from diverse populations to provide definitive guidance.

It is obviously not practical to try to conduct drug trials in every recognized patient population in the world. But we think that developers are missing an opportunity to capitalize on the increase in the number of countries hosting clinical trials. Researchers should be designing studies — and choosing study sites — to make clinical trials more informative about the safety and efficacy of drugs for as much of the global population as possible.

This could mean conducting clinical trials in particular places. Or it could mean increasing the numbers of patients recruited to certain trials. Another option could be to conduct 'ethnobridging' studies. Here a drug that has been assessed in a major clinical trial is then tested on a smaller number of people from a population of interest to gain insights about side effects, appropriate dosing levels and so on for that population. Japan uses this approach a lot: medications deemed safe and effective from global trials are subsequently tested on Japanese patients[10].

Regulatory authorities could do more. Mechanisms for homing in on 'special populations' in drug development are already in place. For instance, the FDA frequently requires developers to conduct a further trial focused on a certain age group if a large proportion of those likely to use the drug in question will be, for example, older than 75. The agency and other regulators could apply similar mechanisms to race or ethnicity. Regulators could also provide guidance for manufacturers on how genetic-ancestry information could be used to expand the assurances for clinicians and patients around drug safety.

Ensuring that more populations are represented in clinical trials might also require that developers, regulators and others address some of the social barriers to enrolment.

Within any one country, some populations might, for cultural or historical reasons, prefer not to engage in a scientific study. Or they might have limited access to the medical centres where clinical trials are being conducted. Currently, some investigators are working to address this, for instance by trying to build trust with communities on their turf. As far as we know, no such efforts are being pursued at scale by regulators or by pharmaceutical companies.

"Most clinical trials do not enrol enough patients from diverse populations to provide definitive guidance."

The ideal would be to match treatments to individual patients on the basis of their genetic, proteomic or other profiles. In theory, that would remove the need to even consider race or ethnicity. With this goal in mind, identifying the individual differences that influence the risks and benefits of a medication should be a component of clinical trials.

For now, however, investigators must at least exploit the fact that clinical trials are being done in many more countries than they were two decades ago — and strive to obtain a more complete picture of disease and how to treat it, to the benefit of all. ■

DOCUMENTING DIVERSITY

Regulatory efforts

Various international endeavours have attempted to provide guidance on how to consider and document population diversity in clinical trials.

The International Conference on Harmonisation (ICH) has produced reports on this issue. The ICH brings together the regulatory authorities of Europe, Japan and the United States with experts from the pharmaceutical industry to create standards for the conduct of clinical trials. The ICH E5 report sets out how to evaluate the impact of ethnicity on a medicine's efficacy and safety. The ICH E17 (released in 2017) offers guidance on planning and designing clinical trials conducted across multiple locations[11].

Similarly, in 2012, it became a requirement in US law that the Food and Drug Administration report on the extent to which demographic subgroups are represented in clinical studies for new drugs, medical devices and biologics such as monoclonal antibodies. The agency has produced reports summarizing these data, including the analysis *Global Participation in Clinical Trials* using data from 2015 to 2016 — an evaluation that is largely consistent with our findings.

Building on these reports, the FDA updated its guidance on how to collect race and ethnicity data in clinical trials. And in 2014, it began releasing Drug Trials Snapshots, public information on participants in the clinical trials that have supported the agency's approval of new drugs (including people's sex, race, age and so on).

These are steps in the right direction. But they have not yet driven a sufficient increase in the diversity of populations represented in clinical trials. T.C.K. & H.L.M.

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Supplementary information accompanies this article online (see go.nature.com/2I224Wm).