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It's time to invite more people to join clinical trials

Drug trials need more participants. Research shows the potential benefits of changing the criteria used to determine who can enrol.

It took Patty Spears, a resident of North Carolina, three attempts to be allowed to participate in a clinical trial for a cancer vaccine to reduce the likelihood that her breast cancer would recur. For the first two trials that she applied for, Spears didn't meet the eligibility criteria – strict guidelines that determine who can participate in a trial. These criteria tend to favour younger, healthier people. Even the third time around, Spears was nearly ruled out because her white blood cell count was barely above the study's minimum requirement.

That was more than 20 years ago. Today, Spears is a patient advocate at the University of North Carolina at Chapel Hill. Along with individuals at other organizations, including the US Food and Drug Administration (FDA) and the US National Cancer Institute, she is part of an effort that aims to expand eligibility for cancer clinical trials. They want more participants to find trials, and more trials to find participants.

The testing of therapies on a wider cohort of participants can increase the safety and efficacy of treatments, especially for those under-represented by medical research, such as older people and those from minority groups. For the funders and organizers of clinical trials, admitting a greater diversity of people potentially means more people taking part in trials. That could mean some trials get concluded more quickly – an important consideration, given that many clinical trials fail to meet their planned timeline for enrolling a full set of participants – and at lower cost.

The effort to expand eligibility is crucial. But it needs more support from funders and regulators around the world. Attempts to gain this support could be helped by the accumulating evidence – including a study published this month in *Nature* – showing the benefits of allowing more people to participate in clinical trials.

Exclusions apply

Most clinical trials have a list of eligibility criteria that must be met before a participant can enrol. These requirements vary from trial to trial and can be designated by investigators, study sponsors and, when they are involved in study design, patient groups. Criteria are devised to protect the safety of participants, so trials might exclude people who are unwell, older or pregnant. Exclusion criteria might also yield 'clean' data – that is, data on people who are more like each other. But it also means that trial participants are less representative of patients – who come in all ages and have a spectrum of health conditions.

> "A more systematic, scientific approach to crafting eligibility criteria could help."

Too often, the requirements are selected simply because the list of exclusion criteria has become a template, carried forwards without scrutiny from one trial to the next. Restricting eligibility in this way can disproportionately affect groups that are already under-represented in medical research. For example, in the United States, diabetes is more common among Black people than white people, and can lead to reduced kidney function. As a result, trials that exclude people with reduced kidney function could disproportionately exclude Black participants.

A more systematic, scientific approach to crafting eligibility criteria could help. In a study published in *Nature* on 7 April, researchers studied the electronic medical records of more than 60,000 people in the United States with advanced non-small-cell lung cancer[1]. The team compared the survival outcomes of people who had participated in clinical trials of drugs for this type of cancer[2] and people who would have been excluded from participating in clinical trials but who had taken the same drugs outside the studies. The results showed that if a more-diverse group of people had been allowed to take part in the trials, the overall survival outcomes would have been almost the same – but that the pool of eligible trial participants would have more than doubled.

In a separate study, pharmacologist Donald Harvey at Emory University in Atlanta, Georgia, also showed that the widening of eligibility criteria is beneficial to trials for non-small-cell lung cancer drugs. According to data presented at a 9 April meeting held by Friends of Cancer Research, a think tank and advocacy group in Washington DC, and the American Society of Clinical Oncology, allowing people with cancers and those with impaired kidney function to take part in trials increased the proportion of participants aged 75 or older from 16% to 22%. This is important, because the majority of people with cancer are older, yet older people with cancer are under-represented in clinical trials.

These studies follow the publication in March of a fresh set of recommendations from the two organizations. Both have been working to re-evaluate commonly used eligibility criteria since 2016 (ref. 3). They are recommending guidelines for making science-based decisions about whether people who are taking or have recently taken other medications should be enrolled in studies. Now that clinical-trial investigators, researchers and funders are taking the first steps towards changing standard practice, regulators must show support. In 2020, the FDA issued guidance to clinical-trial designers regarding criteria such as HIV status and the presence of brain metastases.

This is impressive progress, but it is time for the effort to broaden its reach – beyond cancer and beyond the United States. Explicit endorsement from other regulators and trial sponsors could propel the movement internationally, and further analyses of electronic medical records could help to establish which requirements should be kept and which are superfluous for studies of various conditions. Together, these changes could foster trials that are faster

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and more meaningful for the patients they are ultimately meant to serve.

Widening the criteria for trial participation will take a concerted international effort from investigators, trial sponsors and drug regulators. A more systematic approach, driven by data and greater involvement of patient groups, can and should be used to select participants — not only for cancer clinical trials, but also for studies for other diseases.

1. Liu, R. *et al. Nature* **592**, 629–633 (2021).
2. Fehrenbacher, L., Ackerson, L. & Somkin, C. *J. Clin. Oncol.* **27** (suppl.), 6538 (2009).
3. Kim, E. S. *et al. Clin. Cancer Res.* https://doi.org/10.1158/1078-0432.CCR-20-3852 (2021).

To remedy health disparities, scientists must 'get political'

The pandemic has given scientists a more prominent voice in society. They need to use it to push for better health through equality.

For more than 150 years, scholarship and research have revealed how poor and marginalized communities are disproportionately affected by disease. People are more likely to become unwell if they earn low wages, have few employment protections, live in unsafe environments, receive poor-quality education, or are discriminated against. Whether Prussia's typhus epidemic of 1847–48, tuberculosis outbreaks in the United States in the 1930s or chronic diseases today, researchers conclude that people would live longer, healthier lives if a society's collective wealth could be shared more equally (M. Marmot *Lancet* **365**, 1099–1104; 2005).

Scholars from disciplines ranging from economics to epidemiology and sociology have proposed ideas for how to share the world's wealth (R. G. Wilkinson and K. E. Pickett *Soc. Sci. Med.* **65**, 1965–1978; 2007). But their advice has mostly been disregarded by politicians. This is in part because the idea that the public and private sectors need to have a greater role in reducing inequality has been at odds with the thrust of global politics for at least four decades.

During the COVID-19 pandemic, the successes that scientists have scored with drugs, vaccines and other interventions have given researchers a voice in decision-making. They need to use that position to advocate for policies that would improve social determinants of better health, such as living wages, employment protections and high-quality educational opportunities. In this way, scientists need to 'get political'.

That will require, among other things, scientists to consider how they can best achieve political impact and policy engagement. But advice is on hand. A Feature on page 674 describes how community organizations in one of the poorest regions of the United States, California's San Joaquin Valley, tried to curb COVID-19 in communities of colour by tackling some of the disease's underlying determinants, in part through political engagement.

> **"There are few funding opportunities for researchers whose main objective is evidence-based policy."**

Hundreds of thousands of people in the valley — mainly immigrants — work on farms and in food-processing or meat-packing plants. Compared with California's more affluent regions, wages in the valley are low and labour protections weak. And neighbourhoods of agricultural workers often have poor-quality schools, insufficient clinics and few markets selling healthy food. Some areas even lack clean, running water. A child born in San Francisco is expected to live at least ten years longer than children in many parts of the valley.

State and county public-health officials know this, but are often unable to push local leaders for the necessary policy changes. This is because they are generally hired to carry out the wishes of elected politicians, and their budgets and jurisdictions are therefore determined by those politicians.

But academic scientists are not tied by these constraints. During the pandemic, researchers in the San Joaquin Valley have partnered with grass-roots groups to try to address inequities and push agriculture companies to report COVID-19 outbreaks and protect their employees with face masks and physical distancing. They have also distributed free tests, and provided outreach and financial assistance for under-served communities.

But there are few funding opportunities for such work, or for researchers whose main objective is evidence-based policy — let alone systemic reform — and that, too, needs to change. Funders and research leaders must place a higher value on these types of impact in research-evaluation criteria. Then scientists would have a greater incentive to collaborate with economists and political scientists to devise ways to share wealth and turn around rising inequality. Those who study racism could work with epidemiologists to better understand why economic and political systems have marginalized certain groups of people for decades, and how reparations or other reforms could begin to turn the tide.

They can also work with think tanks to write the short, research-informed reports that are required reading for politicians and policymakers. And they could co-design their studies with grass-roots groups who advocate for — and work with — communities in need.

Scientific discoveries and inventions made during the pandemic have led to progress in diagnostics, therapies and, of course, vaccine production. But the pandemic is far from over, and, combined with economic inequality and climate change, the world is in a precarious era. Now that the pandemic has elevated scientists' voice in society, more must learn how best to use that voice to advance the cause of economic, racial and social justice. Without such change, the essential research that is scientists' main focus will ultimately fall short of achieving its goal of building healthier, more resilient, more equal and more just societies.