

Editorial

COVID-19 and Equitably Sharing of Benefits and Burdens of Research

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An important key principle of research ethics is that the benefits and burdens of research with human participants should be equitably distributed [1]. The question of where COVID-19 clinical trials will be conducted is relevant to both the burdens and benefits of research. On the burdens side, there have long been concerns about the “off-shoring” of studies to low- and middle-income countries (LMICs) to take advantage of looser regulation and of populations eager to participate in research because they have no other good options for accessing health care [2]. This concern explains the outrage sparked by a French doctor's statement that COVID-19 trials should be conducted in Africa to take advantage of the fact that “there are no masks, treatment, or intensive care” (which would presumably make it easier to determine whether the experimental intervention was working) [3]. World Health Organization (WHO) Director-General Tedros Adhanom Ghebreyesus condemned the comment as “a hangover from a colonial mentality” [4]. This principle has important implications for questions about where research will be conducted, how participants will be recruited, what questions will be investigated, and who will control the distribution of any innovations that result. In the rush to initiate clinical trials of treatments and vaccines for COVID-19, careful attention to these questions is particularly important. If clinical trials are not designed with equity considerations consciously in mind, the response to the pandemic may exacerbate disparities in health status between population groups. These substantiate that the principal of benefits and burdens of research with human participants should be equitably distributed.

At the same time, excluding LMICs from COVID-19 research is clearly not the solution, as doing so would reduce the potential benefits of research for persons in those regions. This is because the results of clinical trials conducted in one part of the world are not necessarily applicable to persons living elsewhere, due to differences in genetic makeups, the prevalence of comorbidities, and local health care infra structures [5]. It is therefore discouraging that the WHO's Solidarity Trial, which is comparing the safety and efficacy of four treatment options for COVID-19, currently includes only a few sites in Africa, Latin America, and South or Southeast Asia [6]. The global community must commit to supporting clinical trials in LMICs that contribute to the development of locally relevant interventions, while also ensuring that these efforts do not take resources away from other critical clinical and public health needs.

The manner in which participants are recruited into studies also raises equity considerations. For example, in the United States, there is substantial evidence that African American and Hispanic and Latinx patients are underrepresented among clinical trial participants [7]. This is a problem because, just like people from different parts of the world, people from different racial and ethnic backgrounds may respond differently to medical interventions [8]. While the reasons for racial and ethnic disparities in clinical trial participation are complex, one factor is reliance on recruitment strategies unlikely to generate significant minority enrolment, such as direct recruitment by physician-investigators at academic medical centers [9]. Proven strategies to increase the diversity of clinical trial participants include the development of culturally and linguistically appropriate communication materials, in-person recruitment at free clinics, and the careful use of financial incentives [10]. These and other strategies to overcome racial disparities in research will be

particularly important in Covid-19 clinical trials, given that the disease is infecting and killing African Americans at a disproportionately high rate [11].

Also important is support for research specifically focused on the unique needs of certain subpopulations. For example, residents of nursing homes and group homes for the developmentally disabled have been especially hard hit by the COVID-19 outbreak [12]. Because these populations have suffered a disproportionate share of the burdens of the pandemic, equity requires support for research specifically designed to reduce risk and improve outcomes in these institutional settings. Similarly, studies should focus on the unique needs of other populations that may be excluded from large-scale clinical trials, such as patients who are pregnant.

The looming issue with respect to research on treatments and vaccines for COVID-19 relates to control over any medical products that are developed. In most cases, companies that develop new medical products are entitled to patent them, even when the research is supported in part by government funds. Patents enable companies to exclude competition and charge high monopoly prices, which effectively blocks large portions of the global population from access to these products. This means that, even when individuals assume risks by participating in research that leads to the development of a medical product, they have no guarantee that, once the product is on the market, it will be made available in their community at a price they can afford.

Efforts are already underway to ensure more equitable access to COVID-19 treatments and vaccines. The WHO and some prominent government and industry leaders recently pledged to work together to ensure that “all people have access to all the tools to prevent, detect, treat and defeat COVID-19” [13]. Some companies have committed to making any such products that they develop available on a nonprofit basis [14]. One idea that will be considered at this year's World Health Assembly is a proposal to establish a mechanism for companies to “pool” patents and other intellectual property rights over COVID-19 products, making it easier for developers to access new technologies and for generic manufacturers to produce needed products at an affordable price [15]. Yet, while these are encouraging developments, they remain insufficient. The Trump administration has made clear that it has no interest in supporting any WHO-led initiatives, and, in any event, the WHO lacks the authority to override national intellectual property laws. While voluntary corporate philanthropy is admirable, with more than 100 vaccine candidates currently in development, there is no assurance that the companies making philanthropic pledges will be the ones whose candidate vaccines ultimately succeed.

What is needed is an international governance system to oversee access to COVID-19 vaccines and treatments. Given the fundamental ethical principle of equity in research, advocating for such a system should be a priority for everyone involved in designing, conducting, and funding clinical trials.

Ethical Issues in Placebo Controlled Trials for COVID-19 Vaccines

Multiple candidate vaccines for coronavirus are being evaluated scientifically in a process of unprecedented speed, and thousands of individuals around the world have volunteered to participate in placebo-controlled phase III field trials. If, or when, one of these candidate vaccines is proved to be safe and effective and receives an emergency use authorization by the Food and Drug Administration, will it continue to be ethical to enroll participants in other coronavirus trials that randomize half of them to a placebo? Some statements in the news media have claimed that it would be unethical to randomize anyone to a placebo control in a coronavirus vaccine trial once a vaccine is proven effective. This stance might be mistaken.

There are arguments that the use of placebo controls in candidate vaccine trials in the face of proven effective vaccines for a given disease is unethical because it violates the ethical principle of equipoise, held by many to be a fundamental norm for clinical trials. The equipoise principle requires that no patient should be randomized to a treatment or control intervention in a clinical trial that is known to be inferior to standard medical care. Clinical trials contrary to equipoise are alleged to violate the right of patients to medical care and the duty of care owed by clinicians. Some argue and contended that equipoise is fundamentally flawed in several published articles. The most general problem with equipoise is that it conflates the ethics of clinical research with the ethics of medical care. Ethical standards that govern medical care need not necessarily govern

ethics of clinical trials. However, even if equipoise is a valid norm for clinical research, it doesn't pertain currently to underway or planned coronavirus vaccine field trials.

Subjects in the coronavirus vaccine trials are healthy volunteers, not sick patients seeking treatment in the context of a clinical trial. Health care professionals who administer candidate vaccines within these clinical trials are functioning as researchers, not as clinicians providing standard treatment. Accordingly, randomizing trial participants to placebo when a proven effective vaccine exists does not violate equipoise or their right to medical care. Nor are trial participants in this situation denied a proven effective vaccine when they volunteer and give informed consent for participation in a placebo-controlled trial. After the first, or the first few, coronavirus vaccines have been demonstrated to be safe and effective, it is likely to take a considerable period of time before they become available for most people. Some individuals in the highest risk groups will likely receive priority access once an authorized or approved vaccine is available. This means that insofar as trial participants are unable to access a coronavirus vaccine outside the research setting, they will not be made worse off by trial participation. Indeed, they may be better off in view of a 50% chance of receiving a potentially effective vaccine. Those individuals who do have access to an effective vaccine outside the research setting are free to receive it instead of opting for vaccine trial participation. Others might choose to participate in a placebo-controlled vaccine trial for altruistic reasons despite their ability to otherwise receive access to a vaccine [16].

Some might argue that research participants become patients just by virtue of rolling up their sleeves to receive a shot of a candidate vaccine. While this is implausible, even if true, it doesn't follow that randomizing the individuals to placebo when a proven effective vaccine exists and is accessible violates their right to medical care. The right to medical care (more specifically, the right to receive an effective vaccine), like nearly all rights, is not an absolute, inalienable right. That right can be waived autonomously by individuals giving informed consent to participate in a clinical trial which randomizes them to either an experimental intervention or placebo. This is another reason why the equipoise principle is flawed, as it does not recognize that the right to medical care can be validly waived. Once a proven effective vaccine for coronavirus is developed, part of the disclosure to prospective participants in a placebo-controlled coronavirus vaccine trial is to inform them about this fact and the possibility that they might be able to get access to a vaccine outside the context of research [17].

The ethics of clinical research has generally been understood as essentially a matter of protecting the rights and well-being of research subjects. But this is too narrow an ethical focus. Also central to research ethics are the potential societal benefits from the knowledge to be gained from rigorous clinical research. Continued, socially valuable, placebo-controlled vaccine trials in the face of a proven effective coronavirus vaccine adequately protect subjects when they are designed and conducted in accordance with standards of scientific validity and the participants provide informed consent. The informed consent process affords these individuals the opportunity to decide whether they want to contribute to ethically sound clinical research with significant potential to contribute to population health. In the wake of the coronavirus pandemic raging around the world, it is highly desirable to develop multiple safe and effective vaccines. The most rigorous way to evaluate vaccines is by means of placebo-controlled trials. To put a stop to placebo-controlled vaccine trials once a single vaccine has been proven effective would be detrimental to population health [18].

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