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The Honorable Alex M. Azar II
Secretary of Health and Human Services
Office of the Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Francis S. Collins, M.D., Ph.D.
Director
National Institutes of Health
U.S. Department of Health and Human Services
9000 Rockville Pike
Bethesda, Maryland 20892

Stephen M. Hahn, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Anthony S. Fauci, M.D.
Director, National Institute of Allergy and
Infectious Disease
U.S. Department of Health and Human Services
5601 Fishers Lane
Bethesda, MD 20892

Dear Secretary Azar, Commissioner Hahn, Dr. Collins and Dr. Fauci:

We are writing to urgently request that the U.S. Department of Health and Human Services (HHS) publicly announce that the U.S. Food and Drug Administration (FDA) will not permit and the National Institutes of Health (NIH) will not support any clinical trials during which human subjects — after immunization with an investigational severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine — would be intentionally infected with the novel coronavirus causing the coronavirus disease 2019 (COVID-19) pandemic. This important policy decision is consistent with a recommendation by an NIH-funded advisory group published last week.

We are in the midst of an unprecedented rush by governments and pharmaceutical companies to develop vaccines to protect against the novel coronavirus. To allegedly accelerate the process of developing an effective vaccine, it was proposed in a *Journal of Infectious Diseases* article published online on March 31, 2020, that we employ “challenge studies” that purposely infect healthy people with coronavirus after they have received a potential candidate vaccine. The misleading premise of this proposal is that using such studies could cut many months off the timeline for vaccine development and approval, thus saving thousands of lives.¹

¹ Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. *J Infect Dis.* 2020;221(11):1752–1756. Published online Mar 31, 2020.

To our knowledge, not one of the many current SARS-CoV-2 vaccine development programs involves plans to intentionally infect volunteers with the novel coronavirus. The most important disqualifying reason against such potentially dangerous and unethical studies is the lack of any evidence that such studies will accelerate overall vaccine development. This speed-up premise is not merely unproven, but the multiple additional time-consuming steps, required by the FDA before any intentional human infection trials can occur, would most likely prolong, not accelerate total vaccine development time. Absent any rigorously established speed advantage, the serious potential risks and unethical shortcomings of a human coronavirus infection study are prohibitive.

A review of the problems with human coronavirus challenge studies, just published in the *New England Journal of Medicine (NEJM)* by a group of NIH-sponsored academic and government experts, the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Vaccines Working Group², concluded the following:

Before any vaccine intervention can be tested [in controlled human infection models (CHIMs)], a [virus] dosing strategy must be found that causes predictable infection with minimal disease severity. Since each challenge round would require an estimated 3 weeks for infection and recovery of participants, with an additional week for facility decontamination and analysis, the dose-escalation period is lengthy. Thus, the development of a robust challenge model for testing SARS-CoV-2 vaccines may be 1 to 2 years. Given that SARS-CoV-2 vaccines will enter phase 3 trials imminently, these scientific and technical factors alone make CHIMs unlikely to accelerate the establishment of vaccine efficacy.

The authors of the *NEJM* review raised the additional important concern about conducting human coronavirus challenge studies:

Even with strict facility engineering controls, stringent discharge criteria, and experienced personnel, there is a potential risk of community spread of the challenge virus.

A 2019 review from the FDA's Office of Vaccines Research and Review in the Center for Biologics Evaluation and Research highlighted the understandable difficulty of choosing the optimal potency of the infecting dose for experimental subjects in CHIMs to support vaccine development:

Administration of hyper-potent doses of challenge agents could lead to significant unanticipated morbidity. Conversely, the consequence of administering a sub-potent dose

² Deming ME, Michael NL, Robb M, et al. Accelerating development of SARS-CoV-2 vaccines — The role for controlled human infection models. *N Engl J Med*. 2020 Jul 1. doi: 10.1056/NEJMp2020076. Online ahead of print.

may be inconclusive findings about vaccine efficacy from the challenge study, placing volunteers at risk without justification.³

The FDA review also highlighted the difficult steps that must be undertaken to prepare an appropriate infecting dose for use in challenge studies, including strain selection and characterization, establishing microbial purity, potency testing, determination of stability and other aspects of carefully manufacturing batches of viral inoculations for subsequent human infection studies.

It is noteworthy that the authors of the influential *Journal of Infectious Diseases* article⁴ were only able to project that utilization of challenge studies during SARS-CoV-2 vaccine development would save several months by omitting any details of, or time estimates for, the multiple, often lengthy steps preceding the necessary FDA authorization to begin infecting humans in such challenge studies.

Ethical problems would be insurmountable without clear evidence that a challenge study can accelerate vaccine development and approval. The critical ethical requirements for previous infection challenge studies have been that they are limited to well-understood diseases that are easily curable or self-limited so that the studies could have been stopped, if necessary, and the subjects could have been treated to prevent serious infection-caused illness or death.

Volunteering for a potentially life-threatening study, involving being intentionally infected with the novel coronavirus after receiving the investigational vaccine or a placebo, with an understanding of the disease that is both primitive and changes almost daily, combined with no effective treatment, looks more like a waiver of rights than an exercise of autonomy via informed consent.

Moreover, comparing the risks of such challenge studies, which include death, to the risks of kidney or partial liver donation, as some proponents of challenge studies have done,⁵ is not a useful comparison for several reasons. First, unlike intentional exposure to the novel coronavirus, kidney and partial liver donation are not experimental and have had decades of data to document their risks. Second, unlike SARS-CoV-2 challenge studies, there is no risk to the community from kidney or partial liver donation.

In a recent commentary assessing the ethics of coronavirus challenge studies, renowned bioethicist Ruth Macklin concluded that in the absence of an effective treatment for a grave

³ Ramanathan R, Stibitz S, Pratt D, Roberts J. Use of controlled human infection models (CHIMs) to support vaccine development: US regulatory considerations. *Vaccine*. 2019;37(31):4256-4261.

⁴ Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. *J Infect Dis*. 2020;221(11):1752–1756. Published online Mar 31, 2020.

⁵ Caplan A. Is it ethical to give someone coronavirus to create a vaccine? Yes. *Boston Globe*. May 14, 2020. <https://www.bostonglobe.com/2020/05/14/opinion/is-it-ethical-give-someone-coronavirus-create-vaccine-yes/>. Accessed July 5, 2020.

disease like COVID-19, the risks of challenge studies are too great and ethically unjustifiable.⁶ The well-known bioethicist Arthur Caplan and his postdoctoral fellow Kyle Ferguson responded to Macklin on June 29, arguing that we should be able to weigh the risks to the volunteers against the “enormous social benefits the [challenge studies] promise.”⁷ This unpersuasive argument assumes what is unlikely, if not impossible to be proven: that the challenge trials will save time in the clinical testing of a vaccine, and that the vaccine tested in the challenge trials will ultimately be proven safe and effective. Accelerating approval time has now been debunked.

A new group, 1 Day Sooner, was formed in April to help speed the development of a SARS-CoV-2 vaccine by recruiting volunteers to participate in coronavirus challenge studies.⁸ Josh Morrison, the group’s co-founder and executive director, came across and was impressed by the above-mentioned *Journal of Infectious Diseases* article suggesting that human challenge studies could speed up the development of a SARS-CoV-2 vaccine by months, potentially saving thousands of lives.⁹ Morrison founded 1 Day Sooner with his friends and set up the website 1daysooner.org to recruit people to volunteer for a coronavirus human challenge study. As of July 1, more than 30,000 people had volunteered via the group’s website under the banner, “I am interested in being exposed to the coronavirus to speed up vaccine development.”

On April 20, 35 members of the U.S. House of Representatives sent a letter to two of you, HHS Secretary Azar and FDA Commissioner Hahn, urging you to support the use of challenge trials to speed the development of a SARS-CoV-2 vaccine.¹⁰ Their letter also referred to the erroneous arguments made in the above-referenced *Journal of Infectious Diseases* article as one basis for advocating coronavirus human challenge trials, stating that “Every week of delay in the deployment of a vaccine to the seven billion humans on Earth will cost thousands of lives.”

In summary, there is a pressing need for you to (1) mitigate future pressure from members of Congress for coronavirus challenge studies and (2) reduce the numbers of similarly misinformed people volunteering to be infected with SARS-CoV-2 who now mistakenly believe that infecting humans in such studies is acceptable because they would lead to accelerated vaccine development and approval by explicitly discouraging such unethical studies.

⁶ Macklin R. Human challenge studies for a COVID-19 vaccine: Ethical quandaries. Albert Einstein College of Medicine’s The Doctor’s Tablet blog. May 15, 2020. <http://blogs.einstein.yu.edu/human-challenge-studies-for-a-covid-19-vaccine-ethical-quandaries/>. Accessed July 5, 2020.

⁷ Ferguson K, Caplan <https://www.thehastingscenter.org/accepting-the-challenge-covid-vaccine-challenge-trials-can-be-ethically-justified/>

⁸ 1 Day Sooner. COVID1-9 human challenge trials. <https://1daysooner.org/>. Accessed July 5, 2020. As of July 5, 2020, 30,108 people from 140 countries had volunteered.

⁹ Turk V. Should we deliberately infect healthy volunteers with Covid-19? *Wired*. May 23, 2020. <https://www.wired.co.uk/article/coronavirus-vaccine-challenge-trial>. Accessed July 5, 2020.

¹⁰ Foster B, Shalala DE, Meeks GW, et al. Letter to HHS Secretary Alex M. Azar and FDA Commissioner Stephen Hahn. April 20, 2020. https://foster.house.gov/sites/foster.house.gov/files/2020.04.20_Ltr%20to%20HHS%20%20FDA%20on%20Rapid%20Vaccine%20Deployment%20for%20COVID-19%20-%20Signed.pdf. Accessed July 5, 2020.

Therefore, we urge the HHS Office of the Secretary, FDA and NIH to immediately issue a formal, public statement announcing that the FDA will not permit, and the NIH will not support, any clinical trials during which human subjects — after immunization with an investigational SARS-CoV-2 vaccine — would be intentionally infected with the novel coronavirus causing the COVID-19 pandemic. This statement should adopt the following key findings of the NIH-funded experts published last week:

“[T]he development of a robust challenge model for testing SARSCoV-2 vaccines may be 1 to 2 years. Given that SARS-CoV-2 vaccines will enter phase 3 trials imminently, these scientific and technical factors alone make CHIMs unlikely to accelerate the establishment of vaccine efficacy.”

We would appreciate the opportunity to further discuss this issue with any of you.

Sincerely,

Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen’s Health Research Group

George J. Annas, J.D., M.P.H.
William Fairfield Warren Distinguished Professor and Director
Center for Health Law, Ethics & Human Rights
Boston University School of Public Health