Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19 vaccine research and the trouble with clinical equipoise

Published Online
February 1, 2021
https://doi.org/10.1016/S0140-6736(21)00198-7

Published Online
February 4, 2021
https://doi.org/10.1016/S0140-6736(21)00193-8

More than 1·8 million lives have been lost due to COVID-19. Two frontrunner vaccines from Moderna and Pfizer-BioNTech promise some relief, with data suggesting 95% efficacy,[1] and have been granted emergency use authorisations in several countries.

In an open letter[2] responding to these developments, participants in COVID-19 vaccine trials argued that those who received placebos should be unmasked and given priority access to authorised vaccines. The letter cited the American Medical Association's Code of Medical Ethics, which highlights the importance of minimising the time research participants spend in a placebo group.

For more on the **Code of Medical Ethics** see https://www.ama-assn.org/delivering-care/ethics/ethical-use-placebo-controls-research

Fulfilling these requests could help to foster trust in medicine and research, reward those who take risks for the many, and prevent future harm from COVID-19 for these participants. However, granting these requests also comes with tradeoffs and highlights competing interests inherent in vaccine development. Importantly, these requests also reveal shortcomings in bioethical resources, particularly clinical equipoise conceptualisations.

Clinical equipoise is a state of uncertainty in which the medical community does not agree on the relative merits of trial arms.[3,4] The concept was developed to resolve the conflict faced by clinician investigators who have obligations to both patients and research. With equipoise, when it is unclear whether test or control treatment is best, random assignment to either group of a trial is generally just. Once equipoise is resolved, continuing a trial without changing treatment assignment is unjust, and participants should be given the best treatment option. However, the American Medical Association's Code of Medical Ethics comes with an important caveat: participant time in a placebo group should be minimised as long as scientific integrity is not compromised.

Unquestionably, a state of clinical equipoise existed when COVID-19 vaccine trials began in 2020. It was then ethically permissible for clinician investigators to randomly assign participants to a placebo or intervention group. Now that emergency vaccine is authorised, are we still in a state of clinical equipoise?

The answer to this question is not straightforward. Equipoise no longer exists with regard to preventing COVID-19 symptoms in the short term. With regard to other important outcomes, equipoise remains. No solid data exist on the infectivity of those who have been vaccinated, on how long the vaccine protects against COVID-19, on how that protection might differ across populations, or on the long-term safety profile of the vaccine.[5] A more fine-grained analysis of clinical equipoise is needed to account for cases in which uncertainty in the medical community exists for some outcomes and not for others and to understand how priorities and interests differ across participants and researchers.

JEM reports a grant from Arnold Ventures and provides bioethics advice for Alexion Pharmaceuticals, COVAXX, and Cambia's pharmacy and therapeutics committee. JEM is also cofounder of the non-profit Bioethics International. PF and ALC declare no competing interests.

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Calling for benefit–risk evaluations of COVID-19 control measures

We think government lockdowns cause substantial collateral health damage. For example, hospital admissions in the USA for emergency treatment of acute ischaemic strokes have been substantially lower in February–March, 2020, than in February–March, 2019, resulting in delayed treatment.[1] Compared with a historical baseline, UK nursing homes and hospices saw an increase in the number of deaths between February and June, 2020, associated with acute coronary syndrome (a 41% increase), stroke (a 39% increase), and heart failure (a 25% increase).[2]

The situation is similar for patients with cancer. In German hospitals, cancer cases decreased during the first national lockdown between March 12 and April 19, 2020: by 13·9% for breast cancer, 16·5% for bladder cancer, 18·4% for gastric cancer, 19·8% for lung cancer, 22·3% for colon cancer, and 23·1% for prostate cancer,[3] suggesting that cancers might have been undetected and untreated during this period. In England, hospital admissions for chemotherapy appointments have fallen by 60%, and urgent referrals for early diagnosis of suspected cancers have decreased by 76% compared with pre-COVID-19 levels, which could contribute to 6270 additional deaths within 1 year.[4] Delayed diagnosis and treatment are expected to increase the numbers of deaths up to year 5 after diagnosis by 7·9–9·6%

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for breast cancer, 15·3–16·6% for colorectal cancer, 4·8–5·3% for lung cancer, and 5·8–6·0% for oesophageal cancer.[5]

Government restrictions are disrupting traditional means of support between friends and family members. Physical distancing and contact reduction are causing severe stress to many people and might increase the risk of suicide.[6] In a meta-analysis of the prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic,[7] the prevalence of depression in the months of the pandemic up to May, 2020, was 33·7% (95% CI 27·5–40·6). Between April 22 and May 11, 2020, 795 (78·9%) of 1008 people aged 18–35 years in the USA reported symptoms of depression.[8] Further and stronger restrictions on physical and social contact could lead to a further increase in the prevalence of depression.

We call on all scientists, public health officials, journalists, and politicians to weigh and consider the collateral damage from government COVID-19 control measures and their negative effect on many short-term and long-term health outcomes. While trying to control COVID-19, all aspects of physical and mental health need to be jointly considered. Other life-threatening diseases are being neglected, and patients with these diseases should receive the same timely and appropriate medical treatment as patients with COVID-19.

GK has received honoraria for consultation and presentation from Dr Schumacher. MK declares no competing interests.

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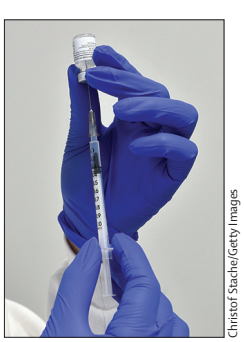
WHO international non-proprietary names: the need to distinguish COVID-19 vaccines

The WHO International Nonproprietary Names Programme would like to highlight that international non-proprietary names (INNs), assigned to well defined pharmaceutical substances, including those used in vaccines, ensure that each substance is recognised globally by a unique and distinct name. Traditional vaccines that are based on live-attenuated or inactivated pathogens are assigned short, descriptive names by the WHO Expert Committee on Biological Standardization. However, new concepts and technologies in vaccine design, such as vaccines based on DNA, RNA, recombinant protein, recombinant virus, and peptides, encompass active ingredients that are well defined and fall within the scope of the INN nomenclature system.[1]

As of January, 2021, several mRNA-based vaccines and one plasmid-based DNA vaccine have been assigned INNs, including the anti-rabies mRNA nadorameran,[2,3] the anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNAs zorecimeran[4] and tozinameran,[4] and the anti-SARS-CoV-2 DNA plasmid reluscovtogene ralaplasmid.[4]

Currently, there are no clear recommendations or a consensus in place regarding the global use of INNs assigned to newly developed SARS-CoV-2 vaccines. National or international legislation usually requires INNs for therapeutic medicinal substances; however, whether vaccines should be included in such requirements is unclear. In the context of the COVID-19 pandemic, this ambiguity has led to a situation in which some vaccine developers have applied for an INN, but others have not. Consequently, INNs for SARS-CoV-2 vaccines are not currently being included in vaccine labels and in most cases are also not listed on the respective regulatory websites.

This lack of information could pose substantial safety issues for individuals who receive a SARS-CoV-2 vaccine during this pandemic, in addition to complicating pharmacovigilance efforts for health authorities. Some of the SARS-CoV-2 vaccine candidates require two injections several weeks apart for maximum protection, which presents a considerable risk if the identity of a vaccine is not globally ensured. Several competing SARS-CoV-2 vaccines are already being distributed and clear identification of each active substance might not always be confirmed. Future scenarios include the use of multiple active ingredients in different formulations and INNs would be the ideal tool to make this approach transparent. The assignment of a unique and distinct INN to the active substances in each



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Published **Online**
February 4, 2021
https://doi.org/10.1016/S0140-6736(21)00099-4