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

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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.

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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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