

# Are Placebo-Controlled Vaccine Trials Ethical Once a Vaccine is Approved?



By Barbara Pfeffer Billauer JD MA (Occ. Health) PhD — November 17, 2020

*Almost 100 years ago, Sinclair Lewis wrote a novel about a doctor trying to elevate scientific discovery over the pursuit of wealth that often accompanies the practice of medicine.*

*The story was about young Dr. Martin Arrowsmith, who discovers a new treatment for bubonic plague. It appears the drug works – but without rigorous controlled experiments, who can be sure? Arrowsmith wants to play by the scientific rules and hold off universal dispensation until he can "prove" the efficacy of the treatment using controlled studies -- all the while people are dying around him.*



Image courtesy of Gerd Altmann on Pixabay [1]

Sounds like today, right? Who can be sure if a vaccine – or indeed any treatment – works in preventing infection or death without controls? Given that some 97.5 of those infected with COVID-19 recover regardless of treatment, merely seeing people recover after being administered a therapeutic and assuming that it cured them – without controls -- can easily be explained by chance. Suppose a touted treatment carries risks of its own. In that case, the risk-benefit calculus

makes use of a risky treatment a very questionable proposition when recovery is quite likely no matter what. Hence, [historically](#) [2], using a placebo methodology was crucial when developing early vaccines, like those for polio, to assure the treatment's efficacy and specificity.

**"...because some technologies have limited previous data on safety in humans, the long-term safety of these vaccines will be carefully assessed using pharmacovigilance surveillance strategies. [NEJM](#) [3]**

Last week, the exciting news from Pfizer would have us believe that a cure is at hand! Interim data indicates the vaccine is safe. But [Pfizer's data](#) [4] is preliminary, not peer-reviewed, relies on a novel technology, and we have no information on the duration of protection or unintended outcomes. Our historical experience is that some safety issues arise once the vaccine is distributed to the general public. It took six weeks for the first cases of Guillain Barre to emerge after the Swine Flu vaccine of 1976 was delivered.

At least eight more vaccine candidates are nearing readiness for human challenge testing [relying on four different mechanisms of inducing antibody response](#). [5] Unlike Pfizer, the other manufacturers have followed the same testing protocol, allowing the pooling and comparison of their results without the need for meta-analysis, thereby providing more robust data sooner than individual studies could. Regardless, the first vaccines will require months of real-world experience to assure their safety and efficacy.

Currently, all vaccine candidates are tested in randomized placebo-controlled trials. But an interesting question has been raised: once we have a putative new vaccine candidate, should we continue to require testing the new candidate against a placebo if existing therapeutics have already proven effective?

**"will it continue to be ethical to enroll participants in other coronavirus trials that randomize half of them to a placebo?" Dr. Franklin Miller**

Dr. Franklin Miller, the quotation's author [1], has advocated continuing placebo-controlled studies even after an efficacious vaccine has been approved. His opponents argue against using placebo controls when a known, safe, and effective treatment exists, relying on the " equipoise " principle, i.e., "that no patient should be randomized to a treatment or control intervention that is known to be inferior to standard medical care."

What is disconcerting about Franklin's view is that he bases his conclusion on comingling concepts of research, clinical, and medical ethics that don't apply to the present situation.

*"[in the doctor's office] the primary goal is to promote the well-being of the individual patient... On the other hand, the goals of clinical research are to produce generalizable scientific knowledge that will improve clinical care for future patients and for society." [2]*

This conflict of interest between clinician and clinician-researcher typically arises in the absence of

satisfactory treatments, where a doctor acts simultaneously as a researcher and as patient-advocate in the form of treating physician. Often this scenario arises in cancer-care cases.

But, in our situation, would any physician ethically recommend a patient accept a placebo if a safe and effective COVID-19 vaccine were available? Certainly, not.

Franklin persists, suggesting that patients can waive medical care, including the option of taking a tested and proven vaccine – the waiver providing an ethical halo to placebo-controlled trials. Maybe. But not in the face of a raging and contagious epidemic, where the patient's well-being is not only of concern to her or her physician, but to society at large. When the primary objective is to prevent all spread, as in a pandemic, rather than produce ivory-tower knowledge, placebo trials serve neither the individual nor the public welfare. Individual rights and waivers fall by the wayside. Even freedom of religion falls in the face of public safety, as determined by the Supreme Court over 100 years ago in the case of *Jacobson v. Massachusetts*, [3] compelling smallpox vaccination even when the objector raised arguments of trespass of his first amendment religious rights.

Franklin next raises the use of informed consent as a protector of patients' rights (if not health), as if this were the *sine qua non* of ethical determinism. But ethically approved clinical studies require much more than informed consent, particularly "fair subject selection" using "scientific objectives, not vulnerability or privilege." [4] Even placebo trials require proper patient selection; they do not exist to serve as a haven for the vaccine averse or those for whom altruism has been romanticized as a societally valid basis to jeopardize one's life, as [Julian Savulescu](#) [6] exhorts for the elderly.

Franklin then turns to a scarcity of treatment – claiming that given expected early limitations of the initial COVID-19 vaccines, many would-be "better off" participating in an experimental vaccine protocol, with at least a 50% prospect of receiving a possibly beneficial experimental vaccine. This, of course, is a last-ditch excuse. We aren't talking here about there not being enough tested vaccines available; we are talking about trying new candidates against existing technology -- or against nothing.

Even in testing new candidates against provably effective ones, ethical issues come into play. [Federal regulation](#) [7] of institutional review boards requires clinical research that minimizes risks, maximizes potential benefits, and presents the value of advanced *knowledge for society that outweighs the risks.*" [emphasis added] In the presence of an effective vaccine, placebo-controlled trials of alternative vaccines become hard to justify.

Astoundingly, Franklin also claims that stopping placebo controls "would be detrimental to population health" and that societal benefits from the knowledge gained justifies the risks. The specific benefits and knowledge that Franklin claims we would be denied remain unmentioned.

On the other hand, one clear harm of the placebo-trial would be infectious spread by those given placebo. A second more nuanced harm raises the banner of societal good and population health over individual well-being - without even specifying the end-goal; a practice similar to the predicate for Nazi medicine. As David Marwell writes in his book on Mengele, the medical philosophy of the time espoused language very reminiscent of champions of clinical ethics at the expense of clinical care: "[The physician] must abandon his old humanitarian conception. He has one patient: the ... people." [5]

Finally, playing into the hands of the anti-vaxxers who scream that vaccines are unsafe -- because some weren't placebo tested, Franklin asserts that "the most rigorous way to evaluate vaccines is employing placebo-controlled trials." Surely, young Martin Arrowsmith would have agreed. But Arrowsmith was paying noble homage to his god of pure science and fleeing the lure of lucrative medical practice. Even so, turning his back on the clamoring crowd of victims in the name of his god of science becomes too much for him.

And so, scientific perfectionism becomes the enemy of good public health, as the unknowingly placebo-ed continue to infect those for whom vaccination is medically contraindicated, the very young, and the very old. And the epidemic continues....

[1] Ethics of Placebo Controls in Coronavirus Vaccine Trials [Hastings Center](#) [8]

[2] [Distinguishing the Ethics of Clinical Research and Clinical Care](#) [7]

[3] "The [Court upheld the authority of states](#) [9] to enforce compulsory vaccination laws. The Court's decision articulated the view that individual liberty is not absolute and is subject to the police power of the state."

[4] Emmanuel Ezekiel, et al., [What Makes Clinical Research Ethical?](#) [10] JAMA Network Open  
DOI: 10.1001/jama.283.20.2701

[5] [Mengele, Unmasking the Angel of Death](#) [11], ISBN 978-0-393-86750-3, p.10

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[1] <https://pixabay.com/illustrations/coronavirus-corona-sars-cov-2-virus-4947692/>

[2] <https://www.acsh.org/news/2020/10/14/testing-polio-vaccine-15084>

[3] <https://www.nejm.org/doi/full/10.1056/NEJM2027405>

[4]

<http://view.email.hcplive.com/?qs=93983f01c306dd4449a866ffaf91215777434df3d37ff4bf348fef9037b9b3eb113bcbd0>

[5] <https://www.nejm.org/doi/full/10.1056/NEJM2027405?query=TOC>

[6] <https://www.bioedge.org/bioethics/the-elderly-can-still-be-heroes-in-the-covid-19-crisis/13411>

[7] [https://escholarship.umassmed.edu/cgi/viewcontent.cgi?article=1218&context=prevbeh\\_pp](https://escholarship.umassmed.edu/cgi/viewcontent.cgi?article=1218&context=prevbeh_pp)

[8] <https://www.thehastingscenter.org/ethics-of-placebo-controls-in-coronavirus-vaccine-trials/>

[9] [https://en.wikipedia.org/wiki/Jacobson\\_v.\\_Massachusetts](https://en.wikipedia.org/wiki/Jacobson_v._Massachusetts)

[10] <https://jamanetwork.com/journals/jama/article-abstract/192740>

[11] <https://www.norton.com/books/9780393609530>