The Ethics of Placebo Trials

Taylor J. McGee '23

Introduction

Peer-reviewed, double blind, and controlled scientific studies make up the backbone of modern scientific epistemology. Before any self-respecting physician, clinician, or researcher dares to begin a course of therapy for a given condition, they must first ensure that there is a significant evidential basis for doing exactly what they are proposing to do. The question remains: why do we not hold all things to this standard? In a 2003 study published in the *British Medical Journal*, researchers found that parachutes were wholly and totally ineffective (Smith). The paper, which was obviously written facetiously, demonstrated the ineffectiveness of parachutes by failing to enroll any members into the group who wanted to *not* use the parachute. While I understand, and will motivate, the fears and concerns of this paper's authors, I, as an apologist for the scientific methodology, feel called upon to defend the foundation of the epistemology to which I am committed.

First, we must discuss the format of a scientific study. For the sake of this discussion, I will be talking about modern clinical studies. The traditional format of a clinical study is that patients enroll in a study and are sorted randomly into two groups. One of the groups is given the experimental treatment, and the other group is a control group of some kind. The doctors or clinicians administering the treatment, experimental or control, would be unaware of which they were administering for any given patient to prevent the administrator's bias from influencing the study. For example, let's say that I develop a drug that might help in the treatment of cancer. After finding clear evidence suggesting this therapy's efficacy in animal studies and preliminary safety trials, I enrolled 300 patients in the trial; half of them get randomly assigned to the group that receives the novel treatment, and half receive a traditional chemotherapy regimen. I then evaluate the tumor response and patient survival rates over the next few months or years. With rigorous and unbiased analysis, the response of patients to my novel drug can be evaluated empirically and objectively in comparison to the response of patients treated with a traditional anti-cancer regimen. In the case that a cohort of patients respond very negatively to my therapy in such a way that threatens the patients, the study may be suspended or discontinued entirely.

Study Design

The format of the study at this point appears to be relatively uncontroversial. The patients knowingly consent to participating in the trial, the trials often require years' worth of animal studies before it can even be considered, let alone approved, by a regulatory agency, and the patients are protected by the regulatory agency's ability to end the trial in case the study ends up going sideways. The complications with this methodology become apparent under two conditions: first, if the standard therapy is quite efficient; second, if the experimental drug is known to be effective. Consider the first case. If the standard level of care is above a certain threshold and there is not sufficient evidence to suggest that the experimental drug would not be as good as the standard of care, it is unethical to attempt the trial in the first place. Going further, if the standard of care is "good enough" then there might be no evidence strong enough to justify potentially taking a course of action that might result in the unnecessary death of a patient. How dare any members of the scientific community dare to sacrifice the life of another at the throne of potentially useless knowledge? Consider the second case. If the standard of care is effectively nothing and the experimental drug shows impressive results in pre-clinical and safety trials, what is the justification of doing clinical trials at all? How dare any members of the scientific community dare to sacrifice the life of another at the throne of scientific rigor?

Objections

The answer to the first objection, that of potentially less effective clinical drugs, is one rooted in the most fundamental principle of medical ethics: informed consent. The justification for doing clinical trials under this condition is the fact that people are willing to do it. People, in full knowledge of what they are committing to, will choose to participate in clinical trials anyway. More philosophically, the threshold of what is "good enough" is one that requires quite a bit of conceptual analysis. Given the incredible uncertainty associated with the right and proper goals of the medical sciences, it would be merely an act of hubris to assert and demand that your conception of "good enough" is objectively the threshold towards which we should strive. This first objection largely falls flat.

The second objection provides a stronger argument against the standard epistemological standards given by clinical trials. To consider the strength of this objection, let us turn to a historical case that involved not administering a potentially lifesaving treatment: Azidothymidine (AZT), also known as Retrovir or Zidovudine. The AZT drug was the first drug approved by the FDA to prevent the progression of HIV infection to AIDS (Corbett). However, there was a significant controversy associated with the initial rollout of the treatment. While it had been shown to be effective in halting the progression of HIV replication in

both *in vitro* and *in vivo* experimentation, the FDA dragged its feet throughout every step of the approval process, causing many doctors to choose not to prescribe the drug at all (Staff; Bernard). Many HIV positive individuals protested the FDA's choice not to expedite the approval of the anti-HIV therapy, resulting in a series of protests that saw the ashes of AIDS victims spread onto the Whitehouse Lawn and the burning of an effigy of Dr. Anthony Fauci (Bernard). AZT had been shown to block retrovirus replication and there was no alternative course of treatment. So the question becomes: What justification could any reasonable person have to the approval of this medication?

History of Azidothymidine (AZT)

A brief discussion of the history of AZT might help flesh out a reasonable response. AZT was an anti-cancer therapy that had been abandoned about 20 years prior to the discovery of its anti-retroviral properties (Corbett). Many leading HIV researchers and physicians had serious concerns that the toxicity associated with AZT made it do more harm than good (Staff). It might be true that AZT has strong anti-retroviral properties; however, it is undeniable that the physiological consequences associated with the consumption of AZT on a regular basis wreaks absolute havoc on the human body (Staff). When a researcher or physician finds themselves in a position where they have a drug with known, incredibly serious toxicities and merely the potential to provide a beneficial upshot, what should they do? Should they attempt to treat with a drug that might actually speed up the death of the patient and significantly decrease the patient's quality of life? Without serious and rigorous studies demonstrating that the benefits of treatment with AZT outweigh the significant costs associated with taking the drug, especially when the calculus had come down on the side of abandonment in other cases, how can a regulatory agency justify the authorization of a drug?

Let us consider another historical case: the first polio vaccine. The Salk vaccine marked the first large-scale placebo-controlled study of a vaccine and set the ethical precedent for nearly all such trials to follow (Meldrum). Of the roughly 200,000 elementary school aged children in the control group of the Salk vaccine study, 115 would go on to be permanently paralyzed and 4 would die, in comparison to 33 paralyses and 0 deaths in the treated group (DeTurk). There were no other polio prevention methods available at the time, and preliminary safety trials, including studies Sabin himself performed in himself and his own family, demonstrated the vaccine to be both safe and effective (Latson). At the time, there were no serious prevention measures in place to protect children from this debilitating virus. The wide-spread vaccine trial delayed the rollout of the polio virus for nearly a year, letting as many as 20,000 children across the country and countless more across the planet become paralyzed in the name of science, not to mention the children who enrolled in the study and happened to get a saline shot by the luck of the draw (DeTurk). Even during the trials of the COVID-19 virus, a patient died because he was infected with the virus after receiving a placebo instead of a vaccine (Simões and Burger). How can either of these trials be morally justified? Dozens of children were paralyzed for life and 4 children died in the name of getting a percentage value. Is that wrong?

If you stop the story of the polio vaccine at this point, the Salk trials would seem to be unjustified. When considering historical events, however, the event must be relayed in its entirety. The Salk vaccine worked by generating live virus and exposing it to formaldehyde to inactivate the viral particles. Inactivated viral particles were then injected into the patients, and the patients' immune system would mount a defense, allowing the patient to better respond to the pathogen should they ever be exposed. While the Salk vaccine protected the individual who was vaccinated, the vaccinated individual could still spread the disease, and had a non-zero rate of paralysis when they came into contact with the virus (DeTurk; Samanthi). A few years later, a different vaccine would be approved for use within the US: the Sabin vaccine. Rather than using inactivated viral particles, the Sabin vaccine attenuated poliovirus strains in non-human cells so that they would be less capable of reproducing in human cells, making them good tools to generate immunity without serious infection (Samanthi). This principle was the basic principle of the cowpox vaccine against smallpox. The Sabin vaccine, unlike the Salk vaccine, was capable of preventing persons who had become infected with poliovirus from spreading the disease while also decreasing the likelihood of serious illness. As with everything, these benefits came at a price: attenuated viruses are more likely to cause disease than inactivated viruses. With the exception of production errors, as seen in the "Cutter Incident," the Salk vaccine could not make a kid sick (Offit). The Sabin vaccine *could* make a child sick, but would do so at a lower rate than natural infection would in a patient treated with the Salk vaccine. Overall, the Sabin vaccine was better suited to eliminate poliovirus and is still the vaccine used today.

Conclusion

When it comes to the generation of public health policy, the primary consideration should be the

medical wellbeing of people. Permitting the prescription of treatment options, whether for cancer, polio, COVID-19, or HIV/AIDS, without the data to justify prescribing the treatments in the first place, is reckless and a direct attack on the medical wellbeing of people. While the system by which we attain data to justify therapeutic prescription is slow and inefficient, in the absence of another means to attain data with such high precision, it must remain in place. One of the common motifs found in ethical discussions is the idea that *ought* should imply *can*. In order for us to have a moral obligation to do something, the thing must be achievable. Public health policy *ought* to protect the medical wellbeing of people, and public health policy *can* do that through the scientific investigation framework. Maybe there is a moral obligation to attempt to formulate a new system that can give the same quality and quantity of data as traditional scientific studies in a more efficient way. However, as I write these words today, there are no means by which a therapeutic option can be justified by data without a traditional peer-reviewed and placebo-controlled scientific study.

REFERENCES

Bernard, Diane. "Three decades before coronavirus, Anthony Fauci took heat from AIDS protesters." The Washington Post 20 May 2020. Digital.

Corbett, Intern Meecha. A brief history of AZT. 9 September 2010. National Museum of American History. 4 March 2022. https://americanhistory.si.edu/blog/2010/09/a-brief-history-of-azt.html#:~:text=AZT%20is%20a%20controversial%20drug.%20For%20example%2C%20some,from%20mother%20to%20child%20during%20pregnancy%20and%20labor.

DeTurk, Dennis. Case study 4: The 1954 Salk Polio Vaccine Trials. n.d. 5 March 2022. https://www2.math.upenn.edu/~deturck/m170/wk4/lecture/case4.html.

Frequently Asked Questions. n.d. 28 2 2022. http://azcc.arizona.edu/patients/clinical-trials/faq.

Latson, Jennifer. "The Vaccine Everyone Wanted." Time 23 February 2015. Digital.

Meldrum, Marcia. ""A calculated risk": the Salk polio vaccine field trials." BMJ (Clinical Research ed.) 317.7176 (1998): 1233–1236. 10 October 2021.

Offit, Paul A. "The Cutter Incident: How America's First Polio Vaccine Led to a Growing Vaccine Crisis." JOURNAL OF THE ROYAL SOCIETY OF MEDICINE (2006): 156–7. Digital.

Samanthi. "Difference Between Salk and Sabin Polio Vaccine." DifferenceBetween.com 15 August 2019. Digital.

Simões, Eduardo and Ludwig Burger. "AstraZeneca COVID-19 vaccine trial Brazil volunteer dies, trial to continue." Reuters 2020.

Smith, Gordon C S and Pell, Jill P. "Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials." British Medical Journal (2003).

Staff, SPIN. "AIDS And The AZT Scandal: SPIN's 1989 Feature, 'Sins Of Omission'." SPIN; 1980s, archive 15 October 2015. Digital.