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LETTER TO THE EDITOR

Placebo Controls: Now???

Arnold I. Caplan[1]

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In this era of a pandemic, why do we need the placebo controls for regulatory agency or Food and Drug Administration (FDA)-approved clinical trials aimed at COVID-19 patients? The answer is always that we have to establish a ruler with a baseline onto which efficacy measurements can be statistically judged. This is certainly a statistically relevant situation when a new drug is being introduced into a medical community and each institution using this drug for the first time can establish their unique, site-specific baseline. In the case of a pandemic where every life matters and most of the wars are being fought in the intensive care units (ICUs), it seems illogical to me to treat patients with placebos as controls. First and foremost, the ICU physicians do not have the time or energy to decide who is going to receive the placebo control. In addition, these healthcare workers are spending enormous amounts of time and energy on each patient to save their lives. In this ethical situation, why not give everyone in the ICU the drug or therapy in question. This represents a uniform treatment policy and the physician has every expectation that since every patient will be getting the experimental drug that it could have a positive effect. In this case, it is true that the physician will have a skewed perspective but be assured that in this pandemic, there will be patients who die and patients who do not survive because they do not respond to that drug or treatment; this should serve as the statistical baseline (Caplan 2018). When the key outcome parameter is whether the patient survives, should not we, in the complex and overcrowded environment of the ICUs, want every patient to be given the same treatment or at least, access to the same treatment regimes. This is exactly what the USA-FDA Guidance proposes for cancer patients (https://www.fda.gov/media/130326/download).

This is not a time for experimental clinical trials; this is a time when healthcare workers are overburdened with keeping people alive. If this is a drug or treatment to be clinically tried in the ICU, let them at it. As a good academic, I fully understand the power of the placebo control. As a potential virus victim, I want full care and that means when I go into the ICU and I signed the consent form, I do not want to be the placebo control nor should the person in the bed next to me be subjected to this academically frivolous activity just to ensure that the outcome is statistically significant to get published in the premier journal.

Give me full care, give me the total focus of the ICU doctors and nurses and give me a chance to beat the virus by not being segregated into the placebo control group, the standard of care for that ICU site should be sufficient. Some of us have gone to offshore clinics and other countries to get appropriate therapeutic reagents because we could not get them in our own hometown hospitals and medical centers because we did not want to be the placebo control. I do not want to show up in the over-crowd ICU with a severe COVID-19 clinical profile to be given a placebo.

This is a time that requires extraordinary efforts on the part of healthcare workers and the innovative and competent medical minds of our society. Please do not burden the ICUs with placebo controls because in this pandemic, it is currently ethically questionable and, at worst, inappropriate.

In Joshua Rothman's article (Rothman 2020), he reviewed Michael Stevens' book on the philosophy of science. Stevens distinguishes between two types of scientific inquiry: In one, the process is consumed by *disproof* where scientists are driven to be the disapprovers, the debunkers, or the destroyers. I call this group "the naysayers". In this type of analysis process, the placebo control required for clinical trials serves as the guiding ruler for judging efficacy. There is, indeed, another approach, a more positive approach, to analyze scientific or clinical progress and that has to do with entering the edifice of new wisdom by going through a new door, a *paradigm shift* (the second Stevens group). These paradigm shifts are painful re-thinking of basic assumptions and in the case of clinical trials, as I have previously outlined (Caplan 2018; https://www.fda.gov/media/130326/download), an expected group of non-responders can provide the floor or

✉ Arnold I. Caplan
aic@case.edu

[1] Biology, Skeletal Research Center, Case Western Reserve University, Cleveland, OH 44106, USA

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base above which a truly efficacious response must exceed. This could be considered as a paradigm shift by eliminating the placebo control.

Such a paradigm shift is required in the use of new technologies like cell-based therapies and, especially, in the case of life-and-death situations (pediatric graft-versus-host disease or in COVID-19 infections). I would argue, in the case of these life-and-death situations, that everyone should be given the same medical treatment and the non-responders could provide the bottom of the ruler by which you can judge efficacy (if everyone survives and walks away, all the better). Placebo controls in these situations, are for me unthinkable, since I would want everyone, myself included, to be given the new and promising procedure or medical intervention (just as President Trump immediately received the experiment drug, REGEN-COV2 and Remdisivir not the placebo control as the clinical trial protocol required). Paradigm shifts are, indeed, hard to articulate and more importantly for the disapprovers and the debunkers, it provides an obstacle rather than the entrance into a new structure, into a new way of taking the same data and seeing it in a different light.

There is no doubt that in any medical intervention, there is the necessity of a placebo control especially if the physician says that this is the new miracle drug and you will be cured of your illness by merely taking this new miracle drug. We know from experience that there is a higher placebo effect from injected material then from just taking a pill. We know this and this necessitates a placebo control to make a judgment of efficacy especially for new drugs. Given a new medical intervention like cell-based therapy (CAR-T or mesenchymal stem cell therapies), it may be that the placebo ruler of drug trials is not appropriate or useful in making a judgment of efficacy. In the drug logic, if a drug is 50% efficacious, it is not considered a fabulous new miracle drug. If it is a life-and-death situation and 50% of the people are saved, I would argue that this 50% saved lives are highly important given that most of these patients would be expected to die. New technologies need to be viewed in a different context. Cell-based therapy cannot, should not, be viewed through a set of criteria designed for the analysis of purified drugs. This new, different context is a paradigm shift. Naysayers beware.

From the Editor

Experimental data on the safety and efficacy of various vaccines and medicines in protection against and treatment of COVID-19 have been accumulating. However, what is badly needed is reliable information on true long-term safety and duration of protection provided by COVID-19 vaccines. Evidently, placebo controlled trials are critical for supplying these data (WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation 2021). Placebo is also being used in clinical trials in mild and moderate COVID-19 cases (Ravikirti et al. 2021; Rocco et al. 2021). Moreover, some groups use placebo controls even in patients with severe COVID-19 (Wang et al. 2020). How to achieve reliable results during the current pandemic crisis in accord with the requirements of evidence-based medicine while minimizing the risks to studies participants? Dr Caplan's may be an important voice of this international discussion.

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