

Placebos in Clinical Trials: Scientific Evidence at the Cost of Patient Well-Being?

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Clinical trials are necessary to prove the safety and effectiveness of new pharmaceutical products and medical devices. The success of new innovation, the outcome of years of research and development, and the profitability of a company lies in the ability of a product to prove clinical worthiness in these trials. If the intent of performing the clinical trial is new product regulatory approval, much emphasis is placed on ensuring that the studies meet FDA requirements. In addition, there is emphasis on obtaining what is known as “level-1 evidence”. This highest level of evidence gives credibility in publications and influences physician adoption and managed care reimbursement. Level-1 evidence requires that at least one properly designed randomized controlled clinical trial be completed¹. In some trials, the experimental treatment is compared to an existing treatment, and in many cases, it is compared to a placebo or “sham” treatment as they call it in the medical device world.

Clinical trial participants are patients with a pre-existing condition or symptoms of a condition who are excited about the possibility of obtaining a promising new form of treatment and have a desire to contribute to science and the advancement of healthcare. When they autonomously provide consent to enroll in a study, they often are asked to accept a randomization process. To be more specific, they acknowledge the fact that they may receive the novel treatment that the study is intended to test, an alternative therapy, or no treatment at all. This leads to an ethical dilemma of when to use placebos in clinical trials. Although a placebo trial may best satisfy the scientific and statistical needs of a study and obtaining level-1 evidence, is the use of a placebo or sham truly in the best interest of the trial participants? Furthermore, does the signed informed consent form, stating that the patient knowingly accepts the risks associated with treatment and sham, justify? and if so – to what extent?

I chose to pursue this topic since I was involved in a clinical trial where the FDA required a minimally-invasive therapy to be compared with a sham treatment². Ordinarily, since the procedure is minimally invasive, I wouldn't have such a big issue with the sham requirement. However, it was the patient population that we were testing that led to my dilemma of whether it was truly the right thing to do. This trial (a) involved patients whose cancer had spread to their bones, (b) required these patients to lie in potentially painful positions to receive the treatment, and (c) had the endpoint of improving end-stage quality of life. Knowing that these patients were going to be followed for up to 6 months, and the chances of them surviving 6 months was slim, wouldn't it be the right thing to do to eliminate the sham and grant everyone the actual treatment knowing that there is potential quality of life benefit?

In the end, after much negotiation and time spent with the FDA, it was decided that "placebo-non-responders", or those in the sham arm, could have a "rescue treatment" and switch over to the treatment arm – but only after two weeks after their sham treatment². It made me wonder if there could be better criteria for determining when placebos should be used and for what populations and study designs. This would be especially prudent in this case since the "blind" nature of the study (i.e. the patient not knowing which treatment was received) was to be revealed if a patient in the sham arm had the opportunity to switch into the treatment arm.

From strictly a utilitarian perspective³, the argument could be made that having less than half of the 147 patients required for the study be randomized into a sham arm would result in a better data analysis and a higher level of evidence. That could potentially make a stronger case for the approval of a novel treatment for (potentially) thousands of patients. However, it is hard to justify that the potential benefits of this study

outweigh the potential hurt, pain, and reduced quality of life for that small group of patients randomized to the placebo sham arm. As such, the perceived net benefit of including the sham requirement may be miniscule or non-existent. Specific to the trial of the bone metastases patients, this point is further supported by the fact that data was available for this patient population, indicating if the “do nothing” approach is chosen, their quality of life is poor and they eventually die. The reason for doing a sham is mainly motivated by the fact that a two-arm clinical study (treatment and sham) is perceived to be a higher level of clinical evidence than a single arm study with comparison to referenced retrospective data. However, the scientific value of this “higher level of clinical evidence” is minimal and should not be at the cost of patient intervention that results in no clinical benefit.

The dilemma becomes amplified when the treatment has the potential to inflict more pain on the patient than if they were to not have participated in the trial. If the sham treatment involves the dying cancer patient to have to spend time away from loved-ones, and to have to undergo treatment preparations and positioning that may inflict pain, then the basic right to “be protected from bodily harm” is violated. It specifically creates an ethical challenge because doctors have an obligation to help people and do what is in the best interest of the patient. That is a much higher priority than doing what is best for a clinical trial or to help a company get a product approved. In most cases, a sham treatment would not contribute any more data than a trial without a sham. From my experience, many investigators refused participation in this bone metastases study, even with the rescue treatment, because they had strong beliefs that the sham arm was harmful and unnecessary. As a result, recruiting sites (and recruiting patients to participate) became a challenge for the study. Keep in mind that this was for a minimally invasive treatment without incisions. The physicians thought lying in an MRI for two hours was unnecessary for someone who was not going to get a real treatment. This example pales in comparison to a study where a sham surgery would result in a physician cutting open someone’s knee but not

actually fixing the joint. I could see even greater ethical challenges with sham surgeries that are a lot more invasive.

There should be some guidelines and recommendations from the FDA, medical societies, and patient advocacy groups as to when it would be appropriate (and ethical) to use a placebo. Alternatives should be considered before mandating a sham treatment in a clinical trial.

- First, it should be determined if existing or retrospective data is available. From a scientific standpoint, comparing a single-arm study to retrospective data is weaker clinical evidence than data from a randomized control trial. However, the question of “how much weaker” is a subjective opinion. As mentioned earlier, obtaining slightly stronger clinical evidence certainly does not justify patient intervention with no clinical benefit, even if it is just a small number of patients to obtain insurance reimbursement (for the majority). Although from a purely utilitarian perspective this may seem acceptable, to me it violates one’s rights to be free from unnecessary harm. If medical journals and insurance companies would recognize the potential for ethical dilemma in some placebo trials, perhaps there would not be such an aggressive mandate for placebo studies as a requirement for publication and reimbursement.
- The second point for consideration is whether there is an existing treatment available. If the current gold standard treatment is something other than “do nothing”, then the new therapy should be compared to the gold standard instead of a placebo. Going back to the bone metastases study, since there are already approved and efficacious treatment options available, I believe that a two-arm study, with the next least invasive option as the comparator, should have been an acceptable alternative to a sham study. The benefits of comparing a new treatment to an existing treatment is also beneficial

from a pricing, coding, and reimbursement perspective as it directly compares the procedure costs and provider time with a known and approved treatment. If the alternative procedure is more invasive (or has greater known risks than the predicted risk of the experimental therapy), perhaps the trial could be designed such that the alternative procedure would only be given in the scenario where the patient did not respond to the experimental therapy – as a “rescue”. From a utilitarian perspective, the overall net benefit of using a gold standard as a rescue treatment exceeds that of a sham trial; and from a basic rights perspective, everyone will have the right to a medical treatment in this scenario.

- Next, a risk/benefit analysis should be performed. If the sham treatment requires the patient to suffer longer than he would otherwise, be in more pain than if she were to not have participated in the study, or be otherwise worse off than doing nothing at all, the sham component should be eliminated. Again, people have the right to avoid harm – in this case, the harm is intervention with known risks but without clinical benefit. An interesting perspective: if a patient will undergo a sham surgery, patients are giving up their rights to be free from harm and receive the best treatment option possible. Since these trials are (usually) randomized, the physician also revokes his/her rights (and obligation) to provide the best medical care possible.
- The condition and status of the patient must also be considered. In the example of the bone metastases patients, these were individuals that had a life expectancy of less than six months, who were already in much pain. This scenario is much different from using a placebo pill on a patient suffering from allergies. The severity of the disease and the life expectancy of the patient must be a factor in determining a need for and justifying a sham treatment. As a side note, throughout this consideration, we also cannot imply that “if you are less sick then it is acceptable to take your right to be free from harm”.
- Finally, the use of sham treatments should not go against the benefit that the treatment being

investigated provides. If a treatment is intended to provide pain relief, the sham should not potentially result in unnecessary pain, even if that unnecessary pain is simply derived from patient positioning or other intervention to simulate treatment. This is analogous to the idea that a placebo pill should not increase the symptoms in which the investigational pill is attempting to cure. From a utilitarian perspective, the whole idea of a clinical trial is to improve the practice of medicine and enable cures that will benefit the aggregate. We should keep in mind that potential harm to a few with no real clinical benefit and subjective scientific merit not only takes away those patients' rights to be free from harm, but may quickly outweigh the net benefit of the trial.

To summarize the above points, the illustration in Figure 1 is a decision flowchart that could potentially be used to determine when it would be ethically appropriate to use a sham or placebo in a clinical study.

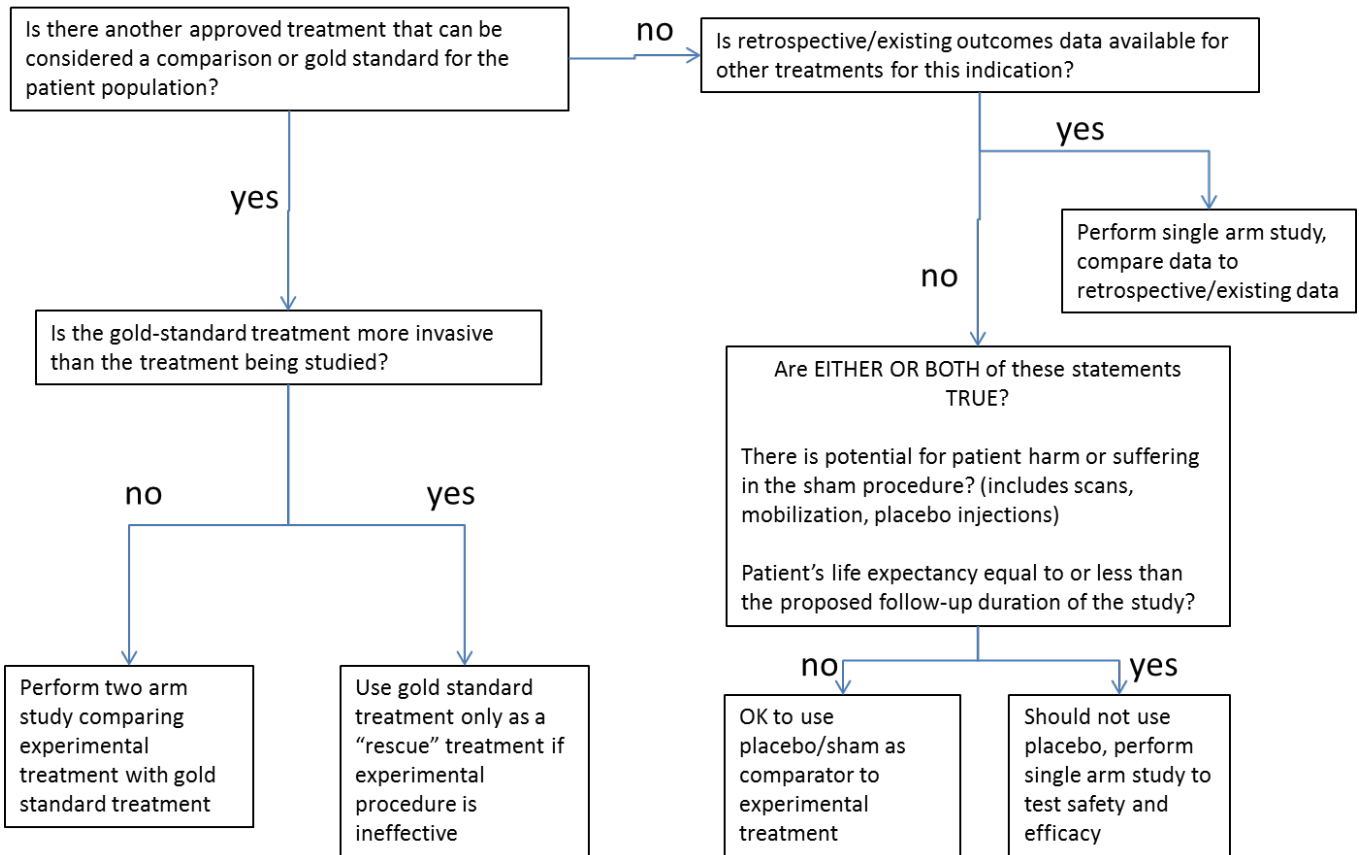


Figure 1 – Algorithm to determine if placebo or sham should be used in a clinical study.

In most cases where an existing treatment is available, it makes the most sense to use that existing procedure as the comparator to the therapy being tested. However, this is not always as easy as it sounds. The idea of a two-arm study with an existing treatment – which would seem like the best option from both the utilitarian and rights perspective - may be met with resistance. This is especially true if there is a potential threat to show that the experimental therapy is superior or even non-inferior to the existing treatment. Consider the case where the “gold-standard” procedure, which would be reimbursed, frequently used, popular amongst physicians – and frankly, one that generates revenue for the provider and hospital, is now being challenged by a treatment that has the potential to be less invasive for the patient. Sure, the potential benefits to the patient are worth studying, but what if this procedure requires less physician interaction, a shorter procedure

time, and could be reimbursed at a lower rate. Worse yet, what if this procedure allows less skilled physicians, or doctors of a different specialty, to all of a sudden be able to treat a particular patient population that was previously only treated by a highly trained physician of a specific specialty. “Turf wars”, potential non-support of a clinical trial, and resistance in using the “gold standard” as a comparator may result. This scenario is intended to illustrate a potential challenge in substituting a gold standard treatment in place of a sham, and shows how the financial and political aspects of medicine often make it difficult to do what would be most ethical based on both the utilitarian and rights theory.

In conclusion, the use of a placebo or sham treatment in a clinical study is a widely accepted practice. Medical journals, payers, and the physician community consider Level-1 evidence with a randomized controlled trial the “holy grail” of published data. However, placebo studies are often designed and even required by the FDA without a careful ethical considerations of whether there are any patient benefit or harm in having the placebo. The algorithm discussed in this paper, consideration of options other than placebo, and a “do what’s best for the patient first” approach to designing clinical studies would be more ethical, and in the long-run, have the greatest benefit to those that clinical trials are intended to help – the patients.

¹Oxford Center for Evidence Based Medicine, <http://www.cebm.net/?O=1025> accessed 8-Jan-2014

²ExAblate Treatment of Metastatic Bone Tumors for the Palliation of Pain, NCT00656305 (details can be found on clinicaltrials.gov)

³McCall, J, A General Introduction to Moral Theory