

Business Ethics – The Use of Placebo-Control Group in Pain Studies

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Joe Crimmins
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A clinical trial practice that has been subject to ethical challenges is the use of a placebo-control group in pain studies.

Background

The use of a placebo-control group when conducting pain studies that are designed to test the safety and efficacy of a new analgesic drug is a practice that is both widely accepted and frequently used.

For U.S.-based clinical trials, the FDA provides guidance for the use of a placebo-control group in clinical studies¹. In its guidance, the FDA proposes,

"In cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo-control."¹

For non-U.S. studies, the International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use (ICH) provides similar guidance as the FDA in the use of placebo-control groups.²

Thus, with some exceptions, it is generally acceptable to use a placebo-control group in clinical trials (including pain trials) that fall outside of the above parameters in order to determine the relative safety and efficacy of a new drug.

Possible Alternative Decisions

Possible alternatives to the practice of using placebo-control groups for pain studies are as follows:

A. Alternative #1 – To have a pharmaceutical company use an active comparator in its pain studies (in lieu of placebo) when testing a new drug.

The rationale is there are many different types of analgesics currently approved and marketed (utilizing many different mechanisms of actions and pain pathways) to address different types of pain. Therefore, one alternative would be to compare the safety and efficacy of the drug that is being tested to an already existing comparator medication (with a similar mechanism of action) that addresses the same target pain pathway.

B. Alternative #2 – No change to current practice.

Continue the currently allowed practice of using a placebo-control arm for the testing of new pain medications in clinical trials.

Stakeholders that Would Be Affected

The stakeholders that would be affected under Alternative #1 are the same as those that would be affected in Alternative #2.

Those Stakeholders are as follows:

1. Patients enrolled in clinical studies that evaluate pain.
2. Pharmaceutical company (the one seeking approval of its pain medication) and its shareholders.
3. The patients who, if the drug is approved, will take the new pain medicine that is being tested once it is approved by the FDA or other regulatory agency.
4. Regulatory agencies responsible for clinical trial oversight and ultimate approval/non-approval of pain medication.

Evaluation of Alternatives #1 & #2 Using Tools of Moral Theory

The following analysis evaluates alternatives #1 and #2 from a Utilitarian Moral Theory and a Rights Theory perspective.

A. Utilitarian Moral Theory Perspective**1. Stakeholder - Patients enrolled in clinical studies that evaluate pain.**

In current practice, patients in a pain study that includes a placebo-control arm may unknowingly (although with the patient's informed consent) receive a placebo that is *known not* to contain ingredients that provide any analgesic effect. Therefore, there is risk that some patients will not experience any pain relief following a surgical procedure (such as dental extraction, knee or hip replacement surgery) during the course of the clinical trial.

Thus, the alternative to use an active comparator analgesic medication (instead of a placebo) to determine the efficacy and safety of the drug that is being tested would be a collective net benefit to EVERY patient in the clinical trial since every patient will know that, regardless of drug randomization, they will receive an analgesic medication (as opposed to receiving a placebo).

2. Stakeholder – Pharmaceutical Company (one seeking approval of its pain medication) and its shareholders.

From the pharmaceutical company's standpoint (the one conducting clinical trials for its pain medication), the alternative to use an active comparator in its clinical trials (instead of a placebo) may have the following effects:

a. Advantages

- The company's drug may be deemed as being more efficacious than the comparator drug that is being used. This may help the marketability of the drug if and when it is approved for sale. This could result in increased revenue for the company.
- The company may experience reduced clinical trial medical costs due to a decreased need for rescue analgesic medicine since there are only active drugs (and no placebo use) in the trial.
- The company and its shareholders may benefit from a financial gain (e.g. stock price) and favorable company image standpoint by exercising its property rights and choosing to ensure all the patients in the pain studies receive chemically active drugs that are designed to provide analgesia.
- The potential financial harm that could result from a company's test drug not being able to show better (or at least equal) efficacy and safety in clinical trials versus an active comparator may incentivize its management to make more careful and strategic R & D choices in deciding how to best utilize company assets. That is, spend money on drugs that will significantly improve a patients quality of life instead of producing a "me too" drug that may offer either no or marginally better efficacy (pain relief) than existing drugs. Management's choice to invest in drugs that significantly improve patient outcomes may yield greater, longer-term financial gains for the company.
- The company, with its policy to use an active comparator in testing drugs for pain relief (in lieu of placebo), may be in a better position to recruit patients to participate in its clinical trials. The rationale is patients would be more likely to enroll in a pain study where they

know that, although they are blinded to which medicine they receive, they are assured of receiving a medication that is either already approved or at least designed to provide analgesia.

b. Disadvantages

- The company may incur additional costs to pay for the active comparator drug to be used in the clinical trials instead of placebo.
- The drug being tested may be deemed as equally efficacious or, worse, less efficacious (as measured by pain relief) versus the comparator drug that is being used instead of placebo. Therefore, there may be no advantage to bring the drug to market if the prospects of the drug being profitable are limited.
- Pharmaceutical companies claim the true safety of the drug being tested can not be assessed if an active comparator is used instead of a placebo.

Since an active comparator would be used instead of a chemically-inactive placebo, the side effects seen in the trials of the tested drug may be caused by either patient perception and or by the chemical components of the drug. Thus, the company would not know which side effects were truly due to the drug being tested.

Mitigating this claim is the fact that the company is required to disclose any adverse events experienced in the trial whether or not the side effects were caused by the tested drug.

Therefore, I do not believe that this is a true disadvantage for the pharmaceutical companies and its shareholders.

Based on the above advantages and disadvantages of using an active comparator (in lieu of a placebo-control), I believe that the pharmaceutical company and shareholders would experience a net collective well being by using an active comparator in its pain studies.

3. Stakeholder - The patients who, if the drug is approved, will take the new pain medicine that is being tested once it is approved by the FDA or other regulatory agency.

From a Utilitarian perspective, the net collective well-being of the patients who ultimately take this pain medication (if approved) will increase if an active comparator is used in lieu of placebo.

The rationale behind this is that the patient who is in need of pain medication will know the true efficacy of the drug since it was compared to an active (already approved and marketed) comparator instead of a placebo.

4. Stakeholder – Regulatory agencies responsible for clinical trial oversight and ultimate approval/non-approval of pain medication.

From the regulatory agencies' standpoint, the advantages and disadvantages for regulating the alternative for a company to use of an active comparator in pain studies (instead of a placebo) are:

a. Advantages

- The ability to better determine the true efficacy of the drug. This will help to ensure an accurate labeling of the drug if and when approved. As a result, the agencies' beneficiaries (the public) will have more data to make more informed decisions when deciding which drug has been proven in clinical trials to provide better efficacy. .

b. Disadvantages

- From the regulatory agencies standpoint, I believe there are no disadvantages to using an active comparator (in lieu of placebo) in a pain study.

Based on the above advantages and disadvantages of using an active comparator (in lieu of a placebo-control), I believe that the regulatory agencies would experience a net collective well being by promoting the pharmaceutical companies' use of an active comparator in their pain studies (in lieu of placebo).

B. Rights Theory Perspective

1. Stakeholder - Patients enrolled in clinical studies that evaluate pain.

One of the main arguments for the use of an active comparator drug in pain studies (in lieu of a placebo) is one that is based on the right to adequate health care (including protection from harm). This, despite the agreement by the patient to informed consent.

In the context of a pain study, I believe the right to adequate health care (including protection from harm) is a derivative (but crucial), positive right in support of the basic right to adequate human life (which includes protection from harm).

The rationale for it being a positive right is that the enrolled patient, pharmaceutical company and investigator know that a placebo does not contain any active ingredients for pain relief. Although the pain that may result from undergoing a procedure which is expected to cause pain (harm) is not life-threatening, it is harm nonetheless.

Therefore, the obligation of the positive right to ensure adequate health care, in this case protection from harm, is assigned to the pharmaceutical company and the investigator of the study.

The foundation for this derivative right is for individuals (patients in this case) to be treated with dignity and respect relative to the drug treatment options that are made available in the clinical study.

The basic right to adequate human life (including protection from harm) that this derivative right supports is that, since there are dozens of existing analgesics on the market for pain relief (with proven and well-established safety and efficacy profiles), there is no reason to use a placebo-control group for a pain trial at the risk of allowing a patient to sustain pain.

The practice of using an active comparator would ensure that pharmaceutical companies and doctors (investigators) are fulfilling their obligation (positive right) to provide the highest quality care for the benefit of the patient.

The basis for the argument that the pharmaceutical company and investigators have a positive right to provide the highest quality care (by using an active comparator in lieu of placebo) to the patient is because:

- the need for pain relief exists,
- the company has the ability to provide an active comparator,
- there is no comparable harm and
- it can be viewed as a last resort.

The patient also has a legal right to informed consent. That is, "Parties to an exchange must freely consent to it, and they must also be fully informed of its conditions".³ This legal right recognizes a patient's autonomy (the capacity to make reasoned, deliberative choices about how to act).

In the case of a pain study, informed consent is the legal documentation provided to the patient informing the patient that they will undergo a medical procedure and be provided adequate health care. The medical procedure will cause pain and, with monetary compensation, the patient agrees to undergo the procedure at the risk of receiving a placebo with no active ingredients that is not designed to provide analgesic relief. Additionally, the patient may receive the test drug which, although designed to provide analgesia, has not been tested to do so.

Finally, the patient is informed that they may receive a test drug, the side effects of that drug are not known. In the event that the patient experiences any side effects the patient will receive adequate medical attention. However, with the monetary compensation, the rights of the individual to seek compensatory and or punitive damages as result of suffering side effects during the clinical trial are either limited and or rescinded.

The patient exercises their autonomy to receive medical care and compensation by participating in a clinical study. Through informed consent, the patient is made aware that they may be receiving a pill that is placebo (known not to contain active ingredients for analgesia).

Although the pharmaceutical company's documentation of informed consent recognizes a patient's autonomy, this recognition of autonomy is a lesser priority right of the patient when compared to that patient's right to receive adequate health care by providing an active comparator drug (in lieu of a placebo) in a pain study. Providing a patient either the test drug designed to provide analgesia or an active comparator that has been proven to provide analgesia supports treating the patient with respect with regards to their humanity.

2. Stakeholder – Pharmaceutical Company (one seeking approval of its pain medication) and its shareholders.

The pharmaceutical company asserts it's legal and property right granted to them by the Regulatory agencies to conduct clinical trials in accordance with standards set by those agencies.

Those agencies do not specify clinical trials where a placebo-control group **should be** used. Rather, the agencies outline standards where placebo-control groups **should not** be used. More specifically, "In cases where an available treatment is known to prevent serious harm, such as death or irreversible

morbidity in the study population..."¹ Therefore, in the case of pain studies (such as dental teeth extraction or hip or knee replacement), placebo-control use to test a new drug falls within the scope of the pharmaceutical company's legal and property rights.

A competing right to the pharmaceutical company's property rights relative to the use of a placebo-control group in a pain study is a patient's right to adequate health care (as previously discussed).

Although informed consent provides the pharmaceutical company the means of allowing it to exercise its property right to test a new drug in patients, I believe this property right is less of a right than the patients' right to adequate healthcare. The rationale is because it undermines the patients respect and dignity as an autonomous individual by allowing the patient to be given a placebo in a pain study when an active comparator could be given instead.

3. Stakeholder - The patients who, if the drug is approved, will take the new pain medicine that is being tested once it is approved by the FDA or other regulatory agency.

From a Rights perspective, the patients who may ultimately take the tested medication may also claim a right to adequate healthcare. This right, however, for these patients may be different than those who may have been randomized to take the unproven drug in the clinical trial. Unlike the patients in the clinical trial, these patients have the autonomy to choose a drug that they feel will best suit their needs. In this case, these patients' rights may be considered as derivative (but less compelling). However, an argument could be made that these patients would not know the efficacy of the drug that was tested if its efficacy (analgesic effect) was compared to that of placebo (as opposed to an active comparator).

Publishing the efficacy results of the tested drug versus an active comparator in a pain trial on the package insert would provide evidence from which the patient could make a better, more informed decision about the true efficacy of the tested drug. Consequently, this data could assist the patient in deciding whether or not to purchase the newly tested pain medication.

4. Stakeholder – Regulatory agencies responsible for clinical trial oversight and ultimate approval/non-approval of pain medication.

From the regulatory agencies' standpoint, the alternative for regulating the use of an active comparator in pain studies (instead of a placebo) benefits the net collective well being of all parties involved in the clinical trial or may be affected by the results of the clinical trial..

Decision about which alternative is best (superior) based on moral theory.

Based on the above analysis of the following alternatives from which to choose:

Alternative #1 – To have a pharmaceutical company use an active comparator in its pain studies (in lieu of placebo) when testing a new drug.

or

Alternative #2 – No change to current practice. (That is, allow pharmaceutical companies to continue to use a placebo control group in pain studies).

I believe the best alternative is Alternative #1 based on a Rights Theory perspective.

References

- 1 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) Guidance for Industry, E 10 Choice of Control Group and Related Issues in Clinical Trials, May 2001.
- 2 The International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use, ICH Harmonised Tripartite Guideline, Choice of Control Group and Related Issues In Clinical Trials, July 20, 2000.

Note: These guidelines were subsequently adopted and implemented by the following:

- i. *EU*: Adopted by CPMP, July 2000, issued as CPMP/ICH/364/96
 - ii. *FDA*: Published in the Federal Register, 14 May 2001, Vol. 66, No. 93, p. 24390-91
- 3 DesJardins, Joseph R., McCall, John J. (2005). *Contemporary Issues In Business Ethics (5th ed.)*. Belmont, CA: Wadsworth, Cengage Learning.
 - 4 Ridgway, Derry (2004). Analgesics for Acute Pain: Meeting the United States Food and Drug Administration's Requirements for Proof of Efficacy, *The Journal of Clinical Pain*, 20 (3), 123-132.