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Therapeutic Misconception, or Not?

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Study subjects often participate in clinical studies because of the "therapeutic misconception" – the belief that a clinical study constitutes medical care, not research. Medical care occurs when a physician provides medical treatment that is specifically designed to benefit the patient. Clinical research occurs when an investigator provides medical treatment in an experiment that (a) will probably not harm the subjects and (b) has the property of equipoise. For some diseases, e.g., certain types of cancer, there are no satisfactory treatments, so the only hope of improving health is through clinical studies. Clinical research is thus the standard of care, but the clinical trials are still primarily experiments. A simple way to differentiate between medical care and clinical research is that if the physician/investigator can assign a specific patient to a specific treatment in the patient's best interests, it is medical care, not clinical research.

It is easy for study subjects – and research personnel – to assume that pharmaceutical companies would not invest in expensive clinical research without a high likelihood of success. The data indicate otherwise: Even if the study subject receives the test article and not a placebo, the chance that an experimental drug will reach the market is only 30% in Phase II and 68% in Phase III.[1]

Equipoise and the Therapeutic Misconception

Bioethicists can argue for hours about subtle nuances in the meaning of the term "equipoise," but, according the definition of "clinical equipoise," it means that the population of study subjects – as a whole – is equally likely to be affected, for better or worse, by the test article (e.g., the study drug) vs. the comparator (e.g., a placebo or standard-of-care treatment). The definition of "theoretical equipoise" is similar, except the rule is evaluated for each individual subject. If the purpose of clinical research is scientific experimentation, clinical equipoise is preferred because it is less prone to selection bias and more consistent with evidence-based medicine. If the purpose of clinical research is medical care, theoretical equipoise is more suitable because it is tailored to the individual. This article employs the clinical version of equipoise, although there are certainly cases in which a clinical trial is the best available medical treatment.

In most cases, determination of equipoise is largely subjective, but can provide at least a rough guideline. (Take-home question: Is a trip to London or Paris better for your health?)

A clinical study may be in equipoise for the subject population, but there will probably be a range of results across the population of study subjects. From the individual subject's point of view, therefore, equipoise provides some reassurance but not a definitive recommendation. Each subject must evaluate the study in the context of his/her individual circumstances. The therapeutic misconception interferes with this evaluation when the subject leaps to the conclusion that, because the study is ethically acceptable for a subject population (i.e., in equipoise), it must be the best choice for his/her individual health.

Some people look at this false reasoning and conclude that the therapeutic misconception inevitably causes study subjects to make incorrect decisions. In fact, it may lead some potential subjects to make the wrong decision (participate in a study when they should not), but others to make the right decision for the wrong reason (participate in a study when they

should). In other cases, potential subjects will make the right decision for the right reason because participating in the study is the best therapeutic choice, i.e. the "therapeutic conception" is correct.

Participating in a study can be the best therapeutic choice in these scenarios:

- There is no good therapeutic alternative to the study, e.g., for cancers that are incurable with standard-of-care treatment.
- The additional medical care provided during the study is superior to the medical care available to the subject outside the study. For example, a person without medical insurance may receive no medical care at all, so the screening activities of history, physical and lab tests may provide a significant, even life-saving, health benefit. In fact, it is not uncommon for screening to discover serious health problems in potential study subjects, which can then be treated. For some subjects, notably the elderly, the human attention afforded during a clinical study can have a salutary health effect.

In these scenarios, there is, in fact, no therapeutic misconception. In the second scenario, there is no therapeutic misconception even if the study drug is no more effective than a placebo.

Example with Two Populations

Imagine a country with two populations: One population ("rich") receives premium medical care and the other population ("poor") receives no regular medical care. Now imagine that an investigator wants to conduct a Phase IV study comparing two approved drugs. The medical literature indicates that one drug is more effective in one group of people, the other drug is more effective in a second group of people, and both drugs are equally effective in a third group. The population is equally divided between the three groups. Each drug has a risk profile that is equivalent overall, but different as to specific side effects. It is impossible, in advance, to predict which drug will be safer and more effective for a specific individual. Based on both safety and efficacy considerations, the study is in equipoise. The study offers premium medical care at the level normally received by rich people.

Rich people probably will not benefit from participating in the study because they already receive premium medical care, including whichever drug their physician believes best for them. In fact, they may be harmed if they are randomized to the wrong study drug. Although the study is in equipoise, rich people should participate only if other motivations, such as altruism, outweigh the risk to their health. If rich people have a therapeutic misconception about this study, they may make an incorrect decision to participate.

Poor people probably will benefit from the study by receiving premium medical care. They will further benefit if they receive a study drug that is safe and effective for them. They may be harmed by a side effect, but that risk was judged acceptable when the FDA approved the two drugs for marketing and the IRB approved the study. Even if they experience an adverse event, they will still benefit overall if the health advantages of premium medical care outweigh the disadvantage of the adverse event. Thus, for poor people, there is no therapeutic misconception. Even if they do not understand that the clinical study is an experiment, participating will probably benefit their health.

This example looks at two populations, one rich and one poor. The same principles apply to other population divisions, e.g., the three effectiveness groups stated above. In fact, every potential subject is the only member of a unique sub-population, so determining whether a therapeutic conception or misconception exists can be very complicated.

The IRB's Dilemma

Should the IRB approve this study for one, both or neither population?

According to the Belmont Report, such questions should be answered using the principles of beneficence, respect for persons, and justice:

- The principle of beneficence suggests that the study should proceed with poor people, who will likely benefit, but exclude rich people, who may well be harmed.
- The principle of respect-for-persons suggests that excluding rich people does not "acknowledge [their] autonomy," i.e., respect their ability to make decisions for themselves. On average, rich people are better-educated than poor people, have better access to medical advice, and are better able to fend for themselves. For example, some rich people may place a high value on altruism and decide to take their chances. Should they be prohibited from participating?
- The principle of justice "is relevant to the selection of subjects of research at two levels: the social and the individual." It says that "people should be treated equally." Traditionally, equal treatment required that both rich and poor should bear the burden of medical research. More recently, it has said that all comers – both rich and poor – should have equal access: the opportunity to participate in a study. However, it allows that the principle of beneficence must be considered in preventing harm to individuals, i.e., rich people in this case. Further, when rich people participate in the study, they may prevent poor people from participating and gaining a likely benefit. Social justice is thus promoted by banning rich people from the study, an injustice in their eyes. On the other hand, poor people may conclude that they are being exploited as guinea pigs, an injustice in their eyes based on a non-therapeutic misconception.

The exercise is left to the reader to approve or disapprove the study, and for which population(s), by deciding which of these conflicting principles, or any other factors, govern.

If the situation were to be reversed between rich and poor people, would your decision be different?

Reference

1. "State of the Clinical Trials Industry", pg. 89, Thomson CenterWatch, 2007

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