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A Conceptual Model for Therapeutic Misconception and Equipoise

By Norman M. Goldfarb

Study subjects often participate in clinical studies because of the "therapeutic misconception": the belief that a clinical study constitutes clinical care, not research. Clinical 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 not harm the subjects and (b) has the property of equipoise.

Bioethicists can argue for hours about subtle nuances in the meaning of the term "equipoise," but it essentially 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., study drug) vs. the comparator (e.g., placebo or standard-of-care treatment). The determination of equipoise has practical limitations, but can provide at least a rough guideline. (Take home question: Is a trip to London or Paris better for your health?)

An oft-neglected factor in these considerations is the difference between the regular care (without drugs) that a patient receives vs. the extra care (without drugs) that a subject often receives. 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 activities to discover serious health problems in potential study subjects, which can then be treated. For some subjects, notably the elderly, the mere human attention afforded during a clinical study can have a salutary health effect.

Figure 1. "TME" Conceptual Model

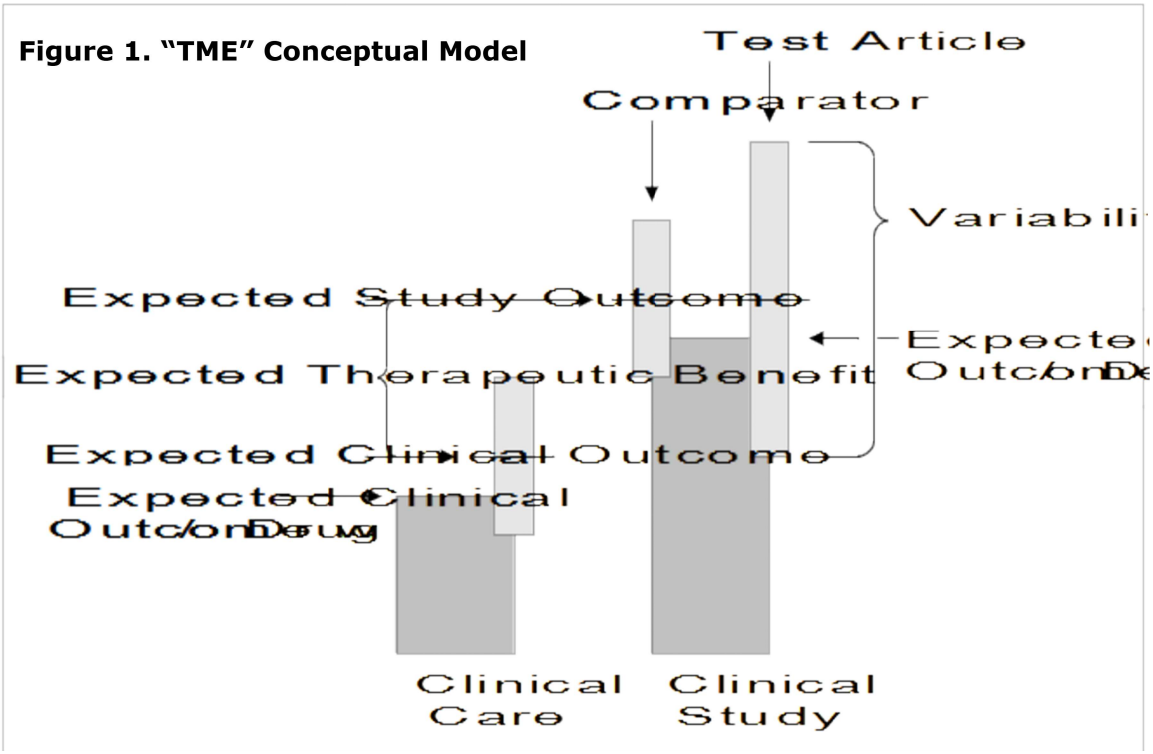

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Figure 1 employs a graphical Therapeutic Misconception-Equipoise ("TME") conceptual model to compare the health affects of a clinical study vs. regular medical care. In this hypothetical example, the subject receives some regular medical care, but receives more during the study. For example, the study may include expensive imaging tests. The standard-of-care medication is also the comparator drug. There is a 75% chance that it will improve the subject's health, but a 25% chance that it will harm it. The test article provides the same likely outcome on average (equipoise), but with more variability because its applicability and dosing has not been fine-tuned in clinical practice.

In this example:

- The average subject is better off in the study than with his/her regular medical care.
- Some subjects will benefit substantially from the study.
- All subjects (whose regular medical care does not include the standard-of-care comparator drug) will benefit from the study.
- Some subjects (whose regular medical care includes the standard-of-care comparator drug) will be harmed by the study.

For subjects whose regular medical care includes the standard-of-care comparator drug, the do-no-harm requirement is met for the average subject but not all subjects. An ethics committee(IRB) may or may not approve this study, depending on the severity of the possible harm.

However, for all subjects whose regular medical care does not include the standard-of-care comparator drug – or any medical care – the study meets the do-no-harm requirement. In this scenario, the therapeutic misconception is, in fact, not a misconception – the subject benefits regardless of which drug he/she receives in the study.

Imagine, if you can, that there is a population that receives no regular medical care. Now imagine that an investigator wants to conduct a study that will not harm – and will certainly benefit the subjects – but is severely out of equipoise. Should the IRB approve the study for this population, or just leave them to their own devices?

The Belmont Report concluded that questions such as this should be answered using the principles of (1) respect for persons, (2) beneficence, and (3) justice:

- The principle of respect for persons does not seem to apply to this question.
- The principle of beneficence suggests that the study should proceed if the subjects benefit.
- The principle of justice presents an interesting dilemma: Subjects without medical care will benefit from participation in the study, while a significant percentage of subjects with premium medical care may be harmed. However, the principle of justice suggests that the investigator should not discriminate against potential subjects just because they have excellent medical care. Although the principle of justice is normally used to protect the disadvantaged, its use here would be to protect the advantaged.

The principle of justice may require that all comers have the opportunity to participate, or that the study not proceed at all. On the other hand, the principle of beneficence requires that the study go forward and the advantaged be turned away. It is left to the reader to approve or disapprove the study by deciding which of these conflicting principles govern, and whether any other factors should be considered. (For example, does it matter if the therapeutic condition under study is chronic or acute?) Beware: if you approve the study for a population without medical care, you may be accused of exploitation.

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The example in Figure 1 is not a run-of-the mill case, but the conceptual model can be applied to any study that involves questions of potential harm, therapeutic misconception, or equipoise.

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