Why Randomized Clinical Trials Are Essential to Informed Medical Decisions

written by Robert McNutt, M.D. | August 9, 2018



I am not a card-carrying philosopher, although I did study philosophy as my undergraduate major. What I enjoyed most was epistemology, the theory of knowledge. We debated, hotly, from the standpoints of social interaction and humanism, “What is knowledge? What constitutes knowing?”

But such philosophical debates are not relevant in medical care. Medicine is not a philosophical province. By that I mean that when we are ill, we are philosophically the same; debating differences is a waste of time. We have equal value; have the same rights to the same efforts and same actions to get us better. The essential issue in medical care is not how we treat each other (kindly, for sure), but what we treat each other with when we are ill. Medical care is a science, and science is how we know.

I am talking here about clinical science, not basic science. Our knowledge of the body continues to advance, informed by basic science, which studies our anatomy and functioning, sometimes to microscopic levels. Consider how our knowledge of genetics is altering how we think about how the body functions, disease manifests, and, ultimately, how to harness new basic science facts to make us better.

In turn, clinical science, rather than being the tool or philosophy that derives new ideas for medical care, is a method that compares new to older ideas about how to better care for people. Clinical science provides facts that we use to make reasoned judgments about whether one treatment is better for us than another, and if that amount of being better is worth the potential added harm that inevitably comes from testing new alternatives. Clinical science is the way we learn if our basic

science ideas have merit.

Randomized Clinical Trials Provide Crucial Information for Clinical Decisions . . .

The “epistemology” of clinical science is the randomized controlled trial (RCT). In previous blogs, I warned about some types of comparisons. Treatments spawned by theory only or observational studies are usually wrong and dangerous. The only clinical science any patient should be exposed to is the RCT.

In a RCT, patients are randomly assigned to one treatment or another. This creates two groups to be compared, one getting the new, and one getting the old treatments. The RCT aims to balance personal and clinical characteristics that may unduly affect the outcome of one group. This balancing is the means by which an adequate comparison of the independent contribution of new treatments may be done.

. . . But Sometimes the Results are Misleading

Even as the RCT provides the anatomical and physiological path to clinical knowledge, however, it can be wrong. The method is not the problem; the problem is applying the method. While we do not expect that everyone be versed in the methodological pitfalls of performing a RCT, a brief overview may help.

Troubles with the Population of Patients Being Studied

The first place a RCT may go wrong is with the population of patients studied. Patients with a disease eligible for a RCT must be gathered for study. There are three populations of patients with disease: the population eligible to be studied,

the population invited into the study and, finally, the population who accepts being in the study. This progression can be problematic. I saw a study, for example, where the eligible population numbered 10,000+, nearly 1,000 were invited into the study, but only 90 accepted. It is hard to imagine that the 90 reflect the 10,000.

Next, for any study, there are eligibility and exclusion criteria for patients who wish to be in the study. For example, some patients may be too sick or have too many other clinical conditions besides the one being studied to be eligible and included. If you have any of the clinical conditions that would preclude you from being in the study in the first place, no RCT will help you make an informed medical decision.

Last, the best way to gather a population of patients for a study is by randomly choosing from all eligible patients who could be in the study. This is often, unfortunately, not the case, and many studies use any patient willing to be studied. Studies requiring large numbers of patients may gather patients from multiple countries and sites within countries. It is always unclear in these situations if the population of patients gathered in this way is similar to others who were not in the study. These populations are called “convenience samples,” and these populations limit the gains in knowledge to all other patients.

Imbalance in Important Clinical Characteristics

Again, the RCT is the best method for clinical comparison because it attempts to balance other personal and clinical attributes that may cloud the comparisons of alternatives. This

is where observational studies fail; they do not balance confounding factors. For example, perhaps a new treatment only works in women who smoke. If there is an imbalance in the number of women who smoke in one part of the study and not the other, we cannot know if what we learn is due to the new alternative treatment or the imbalance of important clinical factors.

RCTs are the best method for balancing, but they are not perfect. By chance, some important clinical factors may end up on one side of the study. It is important to count the numbers of patients with similar clinical characteristics for all compared treatments. While researchers have statistical methods to re-balance populations of patients, these are imperfect, also. Imbalance of important clinical factors even in a RCT must be considered.

Masking

A crucial aspect of comparing alternatives is that neither the patient nor the physician should know who is getting what treatment. This should be true both when patients are randomized and entered into the study, and at the end of the study when outcomes are measured. The term used for this is "masking." Unmasking is a major reason why RCTs fail. This is especially important in RCTs that have "subjective" outcome measures, such as pain or satisfaction. If a patient knows what they are getting, they can alter their true feelings in order to support the researchers, for example.

In a powerful demonstration of the need for masking on patients' perceptions of outcomes, patients were randomized to receive a surgical procedure to clean out arthritic debris from

their knees, or to have a "sham" surgery. The sham surgery made cuts in the skin just like those of the actual surgery, but no procedure was done. This study was conducted because people who had had the surgery said they were much better off after the surgery than before, but these patients chose the action and no comparison had been done. Surprising some, the sham performed as well, and even a bit better, than surgery, raising serious doubts about the value of doing the expensive cleaning of arthritic debris. RCTs with appropriate masking are only way to determine truth from fiction about the values of medical treatments.

Missing Data

Every patient who begins a study must be accounted for at the end of a study. Sometimes people drop out of a study, and they do so in non-random ways. For example, some patients suffer more side effects with a new treatment and then drop out of only the part of the study testing the new treatment. If those who drop out are not considered in the final analysis, the results will be flawed.

How to Know if a RCT Is Relevant for Your Medical Decisions

The only philosophy of medical care, in my view, should be that patients make choices, not physicians or systems of care. But, to make an informed choice, patients must be given evidence that is reasonable enough for making those choices. The only clinical science that fits this bill is the RCT.

Your physician can help you determine if the treatment you are offered has been adequately tested in clinical science. The

population studied must be representative, and you must be similar in terms of your disease with those in the study. In addition, important clinical factors that may affect the outcome of the study must have been balanced for all compared treatments, the assessment of the outcome of the study must be made without knowing who got what treatment, and all patients must be accounted for at the end of the study. If these items have been accounted for, the study is likely useful for your decision-making.

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