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Are Most Clinical Trials Unethical?

By Michel Shamy — May 21, 2018

A premature infant is born with a form of severe lung injury that carries a 20% chance of survival. Her physician decides to throw a medical “Hail Mary” and try an untested adult technique to bypass the injured lungs. The infant survives, and after a few more tries, the physician realizes that the survival rate may be as high as 80% with this new treatment. Does he know enough that the treatment should become standard practice, or is a randomized clinical trial required?

In modern medicine, randomized clinical trials (RCTs) are a very effective way to determine the efficacy of different treatments. In an RCT, patients are randomly assigned to receive one of the treatments under study, and the differences in their outcomes are measured. Randomization can be a very helpful tool to minimize the impact of confounding factors, so that scientists can be as confident as possible that any differences between the groups are due to the treatments and nothing else.

RCTs can work very well, for example in circumstances where scientists are seeking to compare two available drugs for the same problem, such as seizures. However, RCTs are often much more complicated than this, involving comparisons between proven and unproven medicines, or between different approaches to treatment — surgery vs. no surgery, or even hospital-level interventions. Questions about what the comparisons should be, how many patients need to be included, and which patients are best to include can raise difficult problems in study design.

Moreover, clinical trials can create an ethical tension between the interests of current patients and acquiring new knowledge to guide the care of future patients, with the risk that current patients might be harmed in the process. Minimizing this risk is a central goal of the systems and agencies that regulate RCTs, including the Food and Drug Administration and local Institutional Review Boards, as well as researchers and clinicians.

In recent years, one of the main questions that has been encountered in such different fields as

neurology, oncology, and pediatrics is: When do we need an RCT to test a particular treatment?

We can imagine circumstances in which an RCT is not required to answer a given question; for example, an RCT is not needed to demonstrate the value of parachutes to sky divers. Additionally, not every RCT will be ethically appropriate, especially if it involves depriving patients of proven therapies (or parachutes).

Therefore, to render RCTs scientifically and ethically justifiable, certain conditions must be met. But what are they?

Much of the recent literature on the topic of RCT ethics references the concept of “equipoise,” which refers to uncertainty or disagreement in the medical community. Though it is widely cited, “equipoise” has been defined inconsistently, is not universally accepted, and can be difficult to operationalize. Most scientists agree that we should not do another study when the answer is known ahead of time; to do so would be redundant, wasteful, and ultimately harmful to patients. When some estimates suggest that as much as 85% of clinical research may be wasteful, there is a strong imperative to develop clear criteria for when RCTs are necessary. In the absence of such criteria, RCTs that are unnecessary may be allowed to proceed – and unnecessary RCTs are, by definition, unethical.

We have proposed a preliminary set of criteria to guide judgments about whether a proposed RCT is scientifically justified. Every RCT should (1) ask a clear question, (2) assert a specific hypothesis, and (3) ensure that the hypothesis has not already been answered by available knowledge, including non-randomized studies. Then, we examined a sample of high quality, published RCTs and found that only 44% met these criteria.

To be sure, our results don’t necessarily mean that the remaining 56% are unjustified or unethical; rather, our data suggest that the regulatory process for approving RCTs could be strengthened to ensure that only those trials that are absolutely necessary should proceed. That is an ongoing objective of our research about research.

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