

A Commentary on Treatment at Random: The Ultimate Science or the Betrayal of Hippocrates?

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INTRODUCTION

Spyros Retsas, MD,¹ addresses a controversial issue in oncology (and medicine in general): the proper role of randomized trials when treating individual patients. He ultimately concludes, "...the randomized trial emerges as a deficient research tool both on deontologic and methodologic grounds." We have been asked to provide a commentary as a companion to his discussion.

Dr Retsas has divided his discussion into three broad categories, with a corresponding position regarding each category: philosophical (equipose, or absolute uncertainty, cannot exist in clinical practice); ethical (beneficence does not allow the physician to randomly assign patients because randomized clinical trials are not treatment, but research); and methodologic (randomized clinical trials are deficient research).

METHODOLOGY

We begin our discussion with the methodology, because it has implications for the philosophical and ethical questions, and because a major part of the argument by Dr Retsas rests on his conclusion that the randomized clinical trial is a "deficient research tool." In support of this, he refers to authors who have argued that well-designed observational studies provide valid answers just as efficiently as do randomized trials. At the same time, he does note that there is no unanimity, and he provides references to articles supporting the randomized trial as the gold standard. We recommend that the

interested reader review these and other related articles, because it is impossible to address completely the statistical issues in a short commentary.

However, the important distinction between an observational study and a randomized study is that only the randomized study can eliminate selection bias.²⁻⁴ Neither method eliminates variation from patient to patient, so both methods will have some variation from study to study. The important consequence of elimination of bias through randomization is that there is a very high probability that a large randomized trial (or a proper meta-analysis of well-conducted randomized trials) will provide an estimate of treatment effect that is close to the true effect. The same cannot be said of a large observational study (or a meta-analysis of several observational studies). If there is patient selection bias, a large observational study will simply give a precise estimate of the wrong answer (ie, of the bias itself). Although steps can be taken to minimize the bias in an observational study by limiting it to one institution, using concurrent controls, and so on, one still cannot ensure that the method for selecting a patient to receive the treatment is not based in some way on characteristics that may not be measured. Indeed, the assertion by Dr Retsas that the physician's experience and knowledge of the patient is the best basis for deciding on treatment almost guarantees bias in observational studies. It simply is not the case that a randomized trial is deficient on methodologic grounds. In fact, on methodologic grounds, it is nearly always superior to an observational study.

Unfortunately, there are numerous examples of widely held beliefs based on observational studies that have been refuted by large randomized trials. Sadly, these beliefs led to inappropriate treatment of many individuals before the randomized trials were completed. Examples from the 1990s include the Beta-Carotene and Retinal Efficacy study,⁵ which refuted the claim that beta carotene lowers the risk of lung cancer, and the Heart Outcomes Prevention Evaluation Study,⁶ which refuted a similar claim for the effect of vitamin E on the risk of cardiovascular disease.

More recently, three randomized trials⁷⁻⁹ have dispelled the belief that hormone replacement therapy (HRT) reduces cardiovascular risk in postmenopausal women. It is worth noting that the latter trials have also given much more insight into risks and benefits of HRT, and now allow patients and physicians to make informed decisions regarding its use. It would be difficult to overstate the importance of these findings, given that before the completion of these trials, the majority of physicians in North America would have recommended that a postmenopausal woman begin HRT, a decision influenced greatly by the presumed cardiovascular benefit. Hundreds of thousands of women received HRT on this premise and were thus placed in a position of being at increased, not decreased, risk for cardiovascular disease and breast cancer.

An example of a much more aggressive treatment for which randomized trials have not substantiated the large survival benefit of earlier observational studies is the addition of high-dose chemotherapy and autologous stem-cell transplantation to conventional chemotherapy for aggressive breast cancer. Two recent trials failed to demonstrate such a benefit, although the former trial is at an early stage of follow-up.^{10,11}

The above examples show the dangers of relying on observational data and help illustrate why the method of randomization, which prevents such bias, is a methodologically superior approach.

PHILOSOPHY

Turning to the philosophical argument, Dr Retsas notes that a major justification of clinical trials is the principle of equipoise, which requires genuine uncertainty regarding the value of a new treatment. He then argues, "To categorize this information into absolute known or unknown, thereby ignoring degrees of knowledge (better or less known), is a fictitious dichotomy unrepresentative of the realities of everyday clinical practice," implying that equipoise almost never holds and that a physician almost always can identify a preferred treatment.

However, we do not believe that it is the responsibility (or even the right) of a physician to automatically recommend the treatment that he or she might choose if he or she

were the one receiving therapy. When the data do not clearly indicate the best treatment, the physician has an ethical responsibility to tell the patient so. The physician should certainly feel free to state a preference, but should also note that there are physicians with similar knowledge and experience who would recommend a different treatment. Equipoise would seem to go beyond one individual's opinion, particularly if it is based on observation or intuition. Equipoise must take into account all of the evidence—or lack of evidence—that exists for a particular drug or therapy.

Speaking as two cancer survivors buoyed by discussions with numerous other patients, it is our experience that many patients are not nearly as frustrated by uncertainty as they are in dealing with physicians who do not provide the patient with enough information to make an informed choice, and who approach treatment decisions with the belief that the physician knows best and will tell patients which treatment is appropriate.

Using only data available before the completion of the randomized trials described in Methodology,⁵⁻¹¹ we believe the majority of the physicians in the United States would not have met the definition of equipoise put forth by Dr Retsas, and, if forced to choose, would have recommended the experimental regimen. The patients would then have received a treatment that was not efficacious, and no unbiased information would have been gathered. Fortunately, there were enough physicians and patients who, given the data available at that time, were comfortable in saying they were uncertain as to the benefit of treatment, with the result that successful randomized trials were performed and patients can now make more informed treatment decisions.

ETHICS

It seemed to us that Dr Retsas' discussion of the ethical dimension consisted of several specific concerns rather than a general theme, so we will discuss several of his specific points from that discussion.

We do not understand the statement about a patient who declines to participate in a trial being denied all other knowledge preceding the trial. We believe physicians should give their patient access to all information that is known at the time. In fact, we are not aware of anyone who is arguing otherwise. However, we strongly disagree with the argument that telling a patient that there is uncertainty about which treatment is best deprives that person of the ability to make a choice. If anything, knowing about the uncertainty should help the patient make a better, more informed choice about treatment.

The argument regarding a head of state seems to be largely irrelevant. Almost nothing about the care of most heads of state will be similar to that of a typical patient. They

may be flown to the best hospitals in the country, or the world, for consultation with the experts in the field, have work-ups with expensive tests—with no appointment delays—that many patients cannot afford, and they may have nearly constant monitoring that is not available to other patients. Rich and powerful patients will often get care that is not available to the typical patient. Although this may be an ethical issue, it has nothing to do with the ethics of patient randomization.

We disagree with the assertion that physicians, friends, and even the wealthy and powerful would not be enrolled onto randomized clinical trials. Physicians and nurses are major participants in many randomized trials. We both know of physicians, nurses, staff, friends, and spouses who are participating in randomized clinical trials involving standard therapies versus experimental regimens. Indeed, both of us would recommend well-designed clinical trials for our own families and would seek them out for ourselves.

We agree that patients participating in a randomized trial should be told clearly that they are participating in an experiment. This is one of the main purposes of the informed consent process. If one of the arms is a placebo, it should be made clear that if patients are randomly assigned to that arm they will not receive treatment. But if the trial is comparing a standard regimen to one or more experimental regimens, as is the case with most randomized oncology trials, to tell patients that they are not receiving treatment is ridiculous. Once random assignment has occurred, the patients most certainly are receiving treatment. In a well-designed trial, patients in all arms will receive at least the most effective treatment currently known for their condition. In addition, they may receive better monitoring than a typical patient because they are participating in a protocol with specific safety and treatment requirements that are checked by a central oversight group.

CONCLUDING REMARKS

We are not arguing that every circumstance calls for a clinical trial or that observational data should never be used. One should consider many things in determining whether there is a clear-cut choice of an appropriate treatment, including data from randomized trials and data from observational studies, particularly regarding possible side effects.¹² However, when randomized trials are available, we believe they should be presented as an option to patients,

and when data are available from well-designed and well-conducted randomized trials, we believe these data will be more reliable than those obtained in clinical studies. They can provide fairly precise estimates of treatment benefit, a comparison of toxicities, and information about quality of life, duration of therapy achieved, and in some cases, differential effects in clearly defined subgroups.

We certainly are not advocating “...following blindly the *P* value emanating from the randomized trial.” However, we believe that failing to conduct randomized trials when they are appropriate, particularly with a belief that the same data can be provided from observational studies, would be a terrible step backward. Although there will always be a role for physician (and patient) judgment in the choice of a treatment, it is only through good scientific evidence, such as that provided by a randomized clinical trial, that a truly informed choice can be made.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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