In this article (the first of a two-part interview), Benjamin Djulbegovic, MD, PhD, discusses the uncertainty principle in clinical trials, a subject he has written about in The Lancet and elsewhere. Dr. Djulbegovic is associate professor of medicine, Divisions of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida, Tampa.

Oncology News International: What is uncertainty?

Dr. Djulbegovic: Uncertainty is inherent in clinical medicine, although many physicians are unwilling to recognize it. It is this need for certainty that leads to excessive diagnostic testing and inappropriate treatments, which result in ballooning health care costs. Uncertainty can have many grades. It can range from complete ignorance to simply not knowing, say, about the relative benefits and harms of the treatment alternatives.

Our relationship toward uncertainty is an epistemological problem. For example, the uncertainty that we are discussing here—experimental testing within the context of clinical trials—is defined by our previous knowledge (and the quality of that knowledge) such as the existence of available evidence, experience, and biological plausibility about a given treatment. Ludmerer has recently made a compelling case that the failure to train clinicians properly for clinical uncertainty was the greatest deficiency of medical education throughout the 20th century.

ONI: What are the tools used to resolve these uncertainties?

Dr. Djulbegovic: In general, we can deal with uncertainty in several ways, all of which will fundamentally depend on our preexisting knowledge about the value of the treatments to be compared.

In some cases, preexisting knowledge can be accurate, based solely on the experience and inferences of individual practitioners, as, for example, the use of penicillin in the treatment of pneumococcal infections. Reliance on physician experience may also lead to false resolution of the uncertainty, however, such as the 200-year practice of venesection for treatment of bacterial infections.

Another method to help us resolve uncertainty relates to formulation of available clinical strategies according to some normative mathematical model. In recent years, these models have gained increasing popularity in the medical literature, usually presented in terms of decision-analytic or cost-effectiveness analyses attempting to deduce under which circumstances (of the uncertainty) one clinical strategy is better than another.

Techniques for these models have all originated in the mathematical foundation of decision and game theory. Of course, the accuracy of normative models is entirely dependent on the accuracy of the assumptions that underlie the construction of these models.

The third way to resolve uncertainty is to apply the empirical method in a clinical trial. The simplest, yet most powerful method to resolve uncertainty about the relative value of competing treatments is to use the technique of randomization, or the flip of a coin. Properly executed randomization is the only technique available for abolishing selection bias.

Use of randomization and other techniques, such as intention-to-treat analysis and blinding, help ensure comparability between two groups in a clinical trial in all respects other than the study treatment. Then, any outcomes that differ between the groups can be more confidently attributed to the study treatment (or to chance). This, in turn, may help to describe the reduction in uncertainty that was achieved by empirical testing.

ONI: What is the best way to resolve uncertainty?

Dr. Djulbegovic: During the last two centuries, fervent debates have been conducted in scientific
and medical circles about the best methods to resolve uncertainties in therapeutics. The debates have usually focused on the application of physiologic deterministic models vs statistical, empirical methods as the best way to prove whether one treatment is better than another. Matthews has noted that the debate has not been solved within the medical profession but, rather, by society at large, in which the clinical trial empirical method has been institutionalized as the ultimate arbiter for resolution of uncertainty about therapeutics. The FDA law of 1962 essentially stated that no treatment would be approved for use in humans until it had first been tested in humans. This belief that uncertainty is best resolved by empirical testing on patients is also echoed by the Declaration of Helsinki, a leading document guiding ethical principles for medical research involving human beings. This document acknowledges that "medical progress is based on research which ultimately must rest in part on experimentation involving human subjects."

ONI: Why is it important to acknowledge uncertainty?

Dr. Djulbegovic: One aspect of our "quest for medical certainty" remains inadequately articulated: To resolve uncertainty, we first need to explicitly acknowledge that uncertainty about a given therapy does indeed exist. If our preexisting knowledge makes clear that one of the treatments to be assessed is known to be superior to the other, then a clinical trial would not be justified. Nothing new would be learned, and we would be administering a known inferior treatment to at least half of our patients. In other words, if there is no uncertainty, there is no need for clinical research.

ONI: When is it ethically acceptable to enroll a patient in a randomized clinical trial?

Dr. Djulbegovic: A clinical trial is justified only if the patient and clinician are uncertain about which treatment to choose. In this case, in addition to helping resolve uncertainty about the value of competing treatments, enrolling patients into a trial represents the fairest way to choose the patient’s treatment. This realization forms a basis for the scientific and ethical underpinnings for the design and conduct of randomized trials, expressed by the uncertainty principle. This principle states that a patient should be enrolled in a randomized controlled trial only if there is substantial uncertainty about which of the trial treatments would benefit the patient more. It is commonly believed that in human experimentation there is unavoidable tension between the conduct of a trial and the autonomy of the individual, as many authors assert, and that patients are asked to make a sacrifice for the good of others, particularly when it comes to the use of placebo. However, this concern is alleviated by explicitly acknowledging uncertainty as the principle upon which randomized controlled trials are based. As long as we are substantially uncertain as to which treatment is superior, patients do not lose out prospectively and are not required to sacrifice themselves for the benefit of others. Thus, ethically, randomized controlled trials should be acceptable to both utilitarians (who seek to bring the greatest good to the greatest number of patients by ensuring scientifically robust results) and Kantians (who seek to protect and preserve the autonomy of individual patients). If the uncertainty principle is applied, there is no a priori reason to be cautious about entering a randomized clinical trial, because innovative therapies are just as likely as standard therapies to be beneficial or harmful on average. Therefore, the uncertainty principle serves two very important functions: (1) To ensure the ethical conduct of clinical trials and (2) to ensure scientifically robust and unbiased results.

ONI: What about nonrandomized clinical trials?

Dr. Djulbegovic: The uncertainty principle usually applies only to phase III trials. In phase II trials, a formal technique for resolution of the uncertainty does not exist. Instead of comparing the innovative treatment with a randomized control, it is compared with historical data on the "standard" treatment. The patient and physician work on the assumption that they "know" what can be expected if the patient accepts the standard treatment. In a sense, resolution of the uncertainty in phase II trials rests on accepted "common knowledge" about historical data. However, the history of medicine is full of examples of studies in which the use of historical controls resulted in a serious bias, and it is considered a less acceptable method for resolving uncertainty about competing treatment alternatives.

References:
Begg CB, Cho MD, Eastwood S, et al: Improving the quality of reporting of randomized controlled


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