Comment: The Ethos of Clinical Trials

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Professor Royall is to be commended for his paper. He has brought together selected excerpts and ideas from the literature that remind us that there is an ethos associated with randomized clinical trials. However, before discussing the paper, it is worthwhile to put the paper and many of the ethical issues into a broader perspective.

The term ethics may be defined as the rules or standards governing the conduct of a profession. Another definition is that it refers to the moral quality of a course of action. Professor Royall, as well as others he has quoted, have sometimes used the term ethics to refer to both definitions. In my discussion I shall be concerned only with the latter definition. It is important to note that society's view of ethical behavior, in the context of a course of action, changes over time and will continue to change. Furthermore in many situations, ethics may vary with individuals, without either one being labeled as "unethical."

Any review of the literature of the ethics of clinical trials must cite the Belmont Report (National Commission, 1978a). This report has had perhaps the greatest influence during the last decade in influencing the thinking on the ethics of clinical trials. It puts forth three basic principles "that serve as a basic justification for the many particular ethical prescriptions and evaluations of human situations." These three ethical principles have been labeled: *Respect for Persons*, *Beneficence* and *Justice*.

Professor Royall's paper singles out randomized controlled trials (RCT) as an area of special concern with regard to ethical behavior. However, most clinical trials being conducted today are not RCTs. The bulk are Phase I and II studies. The customary usage of these terms is that Phase I trials are situations in which a treatment (usually a drug or drug combination) is to be used on humans for the first time. The object of the experiment is to find doses and schedules having acceptable toxicities. Phase II trials are generally concerned with attempting to find out if a treatment has any beneficial activity. Ideally, only when a Phase II trial results in benefit would a Phase III trial be initiated. A Phase III trial is defined to be a comparative trial in which experimental therapies are compared to best standard treatment or even with other experimental therapies. Phase I trials are never randomized; some Phase II trials may be randomized trials, but most of them are not randomized. Almost all Phase III trials are randomized, but some are carried out without randomization. It is clear in the context of the strategy of clinical investigations, that the Phase I and II studies must precede Phase III studies. It is not surprising that there are many more of these being conducted compared to RCTs.

Nearly all of the ethical concerns which Professor Royall directs at RCTs also hold for nonrandomized trials. Depending on the treatment, the nonrandomized trials may be either an "experimental" or a "demonstrative" trial. The equipoise argument must equally hold for nonrandomized trials. The problem of accumulating evidence as a trial proceeds, which can change a physician's subjective or objective assessment of a particular treatment, also apply to nonrandomized trials. Informed consent is required by the U.S. Code of Federal Regulations (1983) regardless of whether the trial is randomized or not. The physician must describe other available therapies, possible side effects and the patient's right to withdraw at any time. In view of the above observations, a paper on the ethics of RCTs is unnecessarily narrow.

The only ethical distinction between randomized and nonrandomized trials is in the patient consent process. In a conventional randomized trial, the patient cannot be informed of the actual treatment which will be given, but is told that the chosen treatment will be selected using a "chance" mechanism. Colloquially, the randomization is described as "tossing a coin" or allowing a "computer to choose the treatment." As a practical matter, randomized trials will involve a small number of treatments (at most four) as *all* of the therapies must be described to the patient at the time of informed consent. It should be noted that the practice of obtaining informed consent is not universally accepted in most countries of the world. Nearly

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