Comment

William D. Dupont

Royall is to be congratulated for his lucid and provocative paper on a very difficult but extremely important topic. There appears to be near universal agreement that the quality and strength of medical inferences can be optimized by well-run randomized clinical trials (RCTs). These experiments provide the fastest and surest way to improve medical therapy. For this reason, the use of RCTs in medical research is in the best interest of society as a whole. The ethical dilemma that is posed by these studies is that what is in the best interest of society is not necessarily in the best interest of the individual research subject. In weighing the competing interests of the individual and society, Royall comes down hard on the side of the patient. His *personal care principle* dictates that the physician must only consider the best interests of the patient and must totally discount the interests of society if they conflict with those of the patient in any way. If we accept the absolute priority of this principle, then Royall's contention that RCTs are rarely ethical is unavoidable. The key question then in evaluating this paper is whether the personal care principle deserves the weight that Royal gives it.

Perhaps the least convincing part of Royall's paper is Section 2.4. Although throughout the rest of the paper he adheres to an exceedingly strict application of his personal care principle, in this section he appears to accept that physicians may violate this principle when required to do so by law. I would argue that in an ideal society law should be the codification of morality rather than the other way around. For example, the military draft laws required American men to kill Vietnamese in the Vietnamese War. However, few people would argue that those laws in and of themselves provided a moral justification for these acts. Conversely, the morality of the physician reporting a patient with gunshot wounds rests not with the legal requirement to do this, but rather with the premise that the rights of society to apprehend fugitives has a higher moral claim than those of the fugitive to confidential care. Thus, to my mind, you either have to extend the *personal care principle* to apply to all patients regardless of the forensic aspects of their health, or admit that this principle does not have absolute priority in adjudicating the competing interests of different members of society. If, however, you take the latter course, it is unclear to me why the best interests of future patients should not have at least some bearing on the action of physicians in their treatment of you or me today. I will accept that a physician's primary obligation should be to his current patients. But I believe that it is possible to take a reasonable moral stance that stops short of Royall's *personal care principle*. For example, we might adopt the following as an alternative.

> **Acceptable Evidence Principle:** A randomized clinical trial must be stopped prematurely as soon as enough evidence has accumulated in favor of one treatment over another to change the medical practice of a large majority of medical experts. That is, at each interim review of the data, we ask ourselves, "suppose we were to stop the trial and publish now, would our publication in addition with all other information known about this treatment and disease be sufficient to change the standards of medical practice?" If the answer to this question is "yes," then we are morally obliged to terminate the trial and publish. If it is "no," we have a moral justification to continue the trial even though the statistical evidence from our study favors one treatment over the other.

The *acceptable evidence principle* has the following consequence that I find appealing. If I believe that treatment A is better than treatment B and yet know that if I share by evidence with the world many reasonable people will not agree with me, then one of two things must be true. First, I may be wrong and the total evidence may be far less convincing than it appears to me. This would argue in favor of continuing my study to obtain further evidence. Alternatively, I may indeed be right. However, even if this is the case, since all lives have equal worth, it is not clear that I am justified in putting the few lives who are at risk in my current study ahead of the many lives that would be lost in the future if I publish unconvincing results today.

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An interesting example to use in considering the worth of this principle is the University Group Diabetes Project (UGDP). Tolbutamide treatment in this trial was terminated prematurely due to an excess in cardiovascular deaths in tolbutamide-treated patients compared to placebo. At the time of termination, the p value associated with the hypothesis of equal mortality rates from all causes was $p = 0.17$, while that for cardiovascular causes was $p = 0.005$ (UGDP Research Group 1970). According to the personal care principle, this trial not only should have been stopped when it was, but in fact, should have been stopped much earlier when the evidence was far less convincing. However, for a number of reasons, the evidence from the study has not been accepted by a large proportion of physicians (Meinert 1986). As a result, oral hypoglycemics have been prescribed to tens of millions of diabetics since the termination of the tolbutamide arm of this trial in 1969. (Today over 3 million elderly american diabetics take sulfonylureas, the pharmacologic class of drugs to which tolbutamide belongs; W. A. Ray, personal communication.) We are thus left with two possibilities. The first is that the evidence from the UGDP is spurious and that oral hypoglycemics are a reasonable treatment for adult onset diabetes. If this is true, then there was no reason to prematurely terminate the trial. The other possibility is that tolbutamide really does increase cardiovascular mortality over treatment by insulin or diet alone. If this is the case, then the UGDP was stopped to spare the lives of a few tens of patients at a cost of possibly hundreds of thousands of lives of patients treated with sulfonylureas after the trial (these latter deaths being due to the fact that the trial's evidence has been deemed unconvincing by many physicians).

I found Royall's dichotomy between the experimental trial and the demonstration trial to be unsatisfying. My own impression is that virtually all trials are demonstration trials in at least a psychological sense. By the time any treatment reaches the point where a clinical trial is justified, the investigators almost invariably have a deep personal belief in the improved efficacy of their pet treatment. One of the reasons why I support the conduct of randomized clinical trials is that so many of these "demonstration" trials show that the obviously superior treatment is, in fact, no better, or actually worse than the previous standard of therapy. (As T. H. Huxley said, "The great tragedy of Science—the slaying of a beautiful hypothesis by an ugly fact.") For example, consider internal fetal monitors (Freeman, 1990). Fetal hypoxia is a common cause of death or serious morbidity. These monitors can identify babies who are at high risk of hypoxia during delivery, when timely intervention should be possible. Thus a compelling theoretical argument can be made that these devices must result in substantial savings in mortality and morbidity. However, repeated clinical trials have failed to demonstrate the reality of this advantage. Clinical trials are of greatest importance in changing clinical practice when they are used to evaluate well entrenched standard therapies. It is unlikely that the radical mastectomy for breast cancer would ever have given way to more benign treatments without the evidence from randomized control trials (Fisher et al., 1989). The true believer can always find some reason to discount evidence from an observational study that disfavors the use of his favorite treatment. Discounting the results of large well-run clinical trials that reach convincing conclusions is far more difficult.

The use of a play-the-winner adaptive randomization scheme is very rare in clinical research. For this reason the extracorproreal membrane oxygenation (ECMO) trial of high risk infants was perhaps an unfortunate example to choose for a paper that is attacking the ethics of RCTs in general. However, I would agree with Royall that this particular trial was unethical given Bartlett et al.'s (1985) previous success with ECMO and their own belief that conventional therapy was associated with a dismal prognosis. Bartlett's study is also vulnerable to criticism on scientific grounds. Indeed, it is, in essence, a slightly disguised historically controlled trial. Its strength of evidence rests almost entirely on the implicit historical comparison with patients who had done poorly on conventional therapy. A similar trial of aspirin versus Tylenol as treatments for the common cold would have a one chance in ten of achieving 10 out of 10 outcomes in favor of aspirin. This is because the recovery rate from colds is 100% regardless of treatment. However, such an outcome would convince no one that aspirin saves more lives than Tylenol. To claim that a trial with only one patient who received "standard" therapy provides the same strength of evidence as a comparable RCT with equal treatment group sizes is ludicrous.

Another problem with this example is the magnitude of the assumed difference in efficacy between ECMO and state-of-the-art alternative therapy. Truly revolutionary treatment advances are rare. If such advances were the norm, there would be no need for RCTs because the evidence in favor of treatment efficacy would be so obvious. Randomized trials have won their place in modern medical

science because most treatment advances are of a modest evolutionary nature that would be very difficult to detect with even well-run observational studies (Dupont, 1985).

It should also be noted that the contemporary survival rates of patients who did not receive ECMO were not nearly as grim as Bratlett et al. (1985) suggest. For example, O'Rourke et al. (1989) observed a survival rate of 60% for patients on conventional therapy in the early 1980s while Dworetz, Moya, Sabo, Gladstone and Gross (1989) reported a survival rate of 90% in patients who received conventional therapy in 1986. Indeed it is far from clear that Bartlett's group could not have conducted an ethical RCT of conventional design if they had been able to provide the best available non-ECMO therapy as the alternate treatment. (See Lantos and Frader, 1990, for a concise review of this literature.)

In spite of the preceding reservations, the issues raised by Royall cannot be easily dismissed. Patients with serious illness are highly vulnerable, and the task of obtaining truly informed consent from them can be exceedingly difficult. This is particularly true when the patient has the option of receiving either of the treatments under study outside of the trial. Currently we are using an egregious double standard in which new pharmacologic treatments must be rigorously evaluated before they become generally available, while new surgical procedures are immediately offered to anyone with the ability to pay. I believe that society has a right to expect that generally available treatments have known and acceptable levels of efficacy, and that new treatments will be evaluated in a way that will lead to continued progress in medicine. The ethical problems of randomizing a patient to an experimental or standard therapy are greatly simplified if the patient's only chance of obtaining the experimental therapy is by entering the experiment. A truly informed consensus as to the ways in which human experimentation should be performed can only be obtained through public debate and the political process. Perhaps the most reasonable position to take is that the *personal care principle* should be followed except in those situations where a political consensus, codified in law, has been reached to the contrary. Our current laws on experimental medical treatments arose, in part, as a backlash to the snake oil salesmen of the 19th century who victimized countless sick and vulnerable patients with worthless or harmful elixirs. These laws mandate the conduct of RCTs prior to making new drugs available to the general public. I believe that most of the ethical issues raised by Royall could be resolved by applying similar regulations to all medical and surgical treatments. With suitable safeguards to protect human subjects, randomized clinical trials can provide an ethical and the optimal means of advancing medical science in societies that wish to protect patients from the adverse effects of unproven therapies while searching for improved treatments for patients in the future.

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Comment

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I agree completely with Richard Royall's conclusion that in some situations in which clinical investigations are "badly needed... nonrandomized controls are the only ones that can be obtained ethically" (Levine, 1986, pages 185–212). Here I shall comment on two components of the analysis which led him to this conclusion: (1) The values of science are portrayed as distinct from and generally, at least potentially, in opposition to those of ethics. (2) The physician's competent judgment is viewed as the dominant factor in determining his or her responsibility with regard to recommending therapies to the patient.

1. I am aware of no substantive challenge to the widely held conviction that the randomized clinical trial is the most scientifically sound approach to

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