"best available therapy" (Melton et al., 1988). Some have advised patients to enroll in randomized clinical trials with the covert intention of withdrawing if randomized to the "inferior arm" (Marquis and Stephens, 1989). These are not ethically acceptable behaviors and they do not necessarily reflect competent judgments (Levine, 1989).

Suppose there is a randomized clinical trial comparing therapy A with therapy B in the treatment of condition C. Doctor S believes that therapy A is superior to therapy B for condition C. Can Dr. S advise patient P with condition C to enroll in the randomized clinical trial without violating the ethical requirements of the personal care principle?

To that question I would answer "yes" if the randomized clinical trial has been justified according to the concept of clinical equipoise as constructed by Freedman (1987). "A state of clinical equipoise is consistent with a decided treatment preference on the part of the investigators. They must simply recognize that their less-favored treatment is preferred by colleagues whom they consider to be responsible and competent."

What about physicians who consider their colleagues either irresponsible or incompetent? What about physicians who feel they have special insights into the truth about therapies that are not shared within the clinical community? If their insights are based upon scientific evidence, they should present their evidence in an appropriate forum. If they are convinced that a randomized clinical trial is not justified, they should present evidence to support this belief to agencies having the authority to disapprove or terminate the randomized clinical trial.

Physicians are expected to conduct their practices and advise their patients according to standards established by and accepted within the clinical community. This community standard is designed to protect the public from deviant physicians who believe they have special insights into the truth about therapies. By definition, in a state of clinical equipoise, the community standard is that the relative merits of the therapies in such a state are not known.

Thus, a competent physician may, in many cases, offer to a patient an opportunity to consider participation in a randomized clinical trial comparing therapies A and B even though he or she believes A is superior to B without violating the personal care principle. When therapies A and B are in a state of clinical equipoise, the physician's belief regarding the superiority of A is to be distinguished from a "competent judgment."

Comment: Personal and Impersonal Care

Foster Lindley

INTRODUCTION

Doctor Royall has performed a distinctive service in canvassing the most important ethical considerations prompted by the practice of randomizing patients to different therapies in clinical trials. I agree with the thrust of his paper favoring nonrandomized clinical studies and will comment briefly on some of his arguments while adding my own. I am hoping that more reflection by investigators on why it is that chance is so important to them will make alternative procedures seem less threatening.

First, a personal note. I came upon James Ware's article "Therapies of Potentially Great Benefit: ECMO" in the November 1989 issue of this journal, by chance. I was so affected by what was said, as well as how it was said, that I could not complete it in a single sitting. If it had not been for the comments by Berry and Royall, thanks to the editorial format, I would have concluded that I simply misunderstood it. I did not realize that decisions regarding alternative statistical strategies, like decisions regarding alternative therapies, have themselves become matters of life and death. That people die in the service of abstract, controversial, statistical proofs, I cannot accept. That they die at the hands of physicians who mistakenly prefer one therapy to another, I can accept. Some will see an inconsistency there; I do not.

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ANY PARALLEL TRIAL IS IMPERSONAL

With the exception of the brief paragraph at the close, which I hope he will expand in his rejoinder, Royall's objection to the randomization principle is

not theoretical, but moral and practical, the emphasis being on the moral. While his concern with the moral issues is apposite, it should be noted that any parallel trial can raise a moral question. When two or more patients in approximately the same condition are to be given different therapies, the physician must be willing to prescribe a procedure she would not otherwise prescribe. This holds whether or not the therapies are allocated at random. The alternatives discussed by Royall, the historical and concurrent comparisons, whereby "every baby in the study would be receiving what his physician considered to be the best care that he could deliver," avoid the moral issues, not merely because randomization is eliminated, but because the physician is providing personal care. Randomization entails impersonal care, but not all impersonal care involves randomization.

WHY RANDOMIZE?

Before taking up some of the more traditional reasons for randomization given by Byar et al. (1976) and discussed by Royall, I will mention some which I believe to be significant.

DON'T BELIEVE IT. OLD

Randomization and a Sense of Responsibility

Randomization is, after all, what gamblers do. I do not know how many people can gamble, but I can; moreover, I know how and why I gamble. With the aid of gambling devices I can adjust my perspective, my attitude and thus my behavior. I can make commitments I could not bring myself to make otherwise. When, on little or no evidence, I make an investment and succeed, my self-esteem is enhanced, and when I fail it suffers. Not so with gambling; my allowance, but not my self-esteem, is at risk. When I am able to make my "play" indiscriminately, I attribute my wins and losses to good luck or bad luck, not to my intelligence or my stupidity. When the "call" is prompted by a principle that does not differentiate between the outcomes, I feel no responsibility for the consequences. The psychological effect is immediate, not deliberate, not mediated by reason. The effect on my self-esteem when an investment fails is likewise immediate, and that is what I avoid. Also, it is my self-esteem that is secured, not the esteem others may have for my behavior. And it is my sense of responsibility for the consequences that I avoid; others may or may not hold me responsible.

The gambling device is used only to achieve a particular state of mind, and once achieved it is no longer dependent on the device. If I do not know of the substitution, I can gamble on a two-headed coin as easily as a standard coin. It is not important that the device actually have two or more outcomes, but it is important that I have two or more options. The call is both explicable and random because the principle on which it is based does not differentiate between the options. Seeing a red hat may prompt me to play the red at roulette as I would have played the black had the hat been black. As my call is both random and principled and as I know the outcome could be known with causal analysis, to gamble I need not fantasize that the causal order is undone. The decisions, to restrict my experience to repeated trials and to employ a device constructed so that no factor effecting the outcome differentiates between the outcomes of interest to me, are my own. I follow the protocols willingly; it is how I detach my intellect to protect my self-esteem while making commitments playfully. As my self-esteem is not at risk and The House will win in the long run, it is largely a matter of how much excitement I wish to purchase. What varies, according to my luck, is the length of time I am able to play.

A Time-Honored Strategy

Avoiding a sense of responsibility for difficult choices by randomization is an ancient practice. Biblical references to the casting of lots when the principals are faced with awesome decisions show how the decision and the responsibility for the decision are being transferred to God: "... the rest of the people also cast lots, to bring one of ten to dwell in Jerusalem the holy city, and nine parts to dwell in other cities" (Nehemiah 11:1); "And Joshua cast lots for them in Shiloh before the Lord" (Joshua 18:10). One reason for discontinuing the practice was that when lots were cast God was compelled to respond, His hand, forced. Merely to seek His guidance was considered more seemly, and, certainly, more responsible. But the temptation to resort to randomization when confronted with momentous decisions, that is, the temptation to avoid "playing God" is at least as strong as it ever was.

The physician may randomize for many reasons, but by doing so, she is able to effect a state of mind whereby she has no sense of responsibility to a patient for a given allocation. The clinician is not, as a matter of fact, making the judgment that a given therapy is the most effective for a given patient, just as a gambler is not making the judgement that the black will appear although the physician does administer the therapy and the gambler does place the chip on the black. Chance selects the therapy and chance selects the color so neither

have a sense of responsibility for the outcome. The moral issue raised by the parallel trial can be, with randomization, anesthesized as the less fortunate patient is selected not by the investigator, but by chance. With randomization the physician is able to design trials she would otherwise find unbearable. Unlike the patient, who may give her informed consent for the trial to proceed, the physician may consent on the condition that her judgment not be at risk.

An Earnest of the Investigator's Detachment

Also, by randomizing the allocation of patients to this or that treatment, the investigator proves to herself and to her peers that she has not, even unknowingly, allowed the personal care principle to degrade the integrity of the trial. By eliminating her subjective judgment she lends an aura of objective detachment to the procedure, the dispassionate stoicism of the gambler. She must show that she places detachment before her oath as a physician even if she, at that time, believes the two therapies to be approximately the same, both in their therapeutic effect and in their side effects, i.e., she is in a state of equipoise.

TRADITIONAL REASONS

Of course, it may be that while the investigator avoids a sense of responsibility for some of the awesome consequences of the trial, she randomizes for other reasons as well, the reasons given by Byar et al. and discussed by Royall.

Selection Bias

First is the oft-made claim that randomization precludes selection bias. And it does preclude any bias that might have been due to the investigator. Not being a factor, the judgment of the investigator is not a differentiating factor. Of course, it does not preclude any other bias and may introduce a differentiating factor that would not be there otherwise. Perhaps the investigatór has sometimes confused avoidance of bias with avoidance of a sense of responsibility for such bias as may by chance occur.

Leaving Validity to Chance

Randomization has an epistermological downside that is seldom mentioned. In leaving the selection to chance to avoid personal involvement, the validity of the parallel trial is also being left to chance. Of course, this holds only for the random elements of the trial; insofar as the patients have been stratified, the judgment of the investigator is involved and responsible. The validity of the trial is contingent on the symmetry of the groups; if they consisted solely of carefully selected matched pairs and if one of each pair were randomized to a therapy, automatically allocating the other patient to the other therapy, the symmetry of the trial would not be left to chance. But if the stratification of the groups is not that exhaustive, the symmetry of the trial is also being left to chance.

Unknown Covariates

Second, randomization is said to balance the groups with respect to covariates, particularly the unknown covariates. But this feature does not become significant until n is relatively large, that is to say, the investigator's anxiety with respect to the unknown covariates is inversely proportional to n. Increasing n, when it involves more phone calls or more bell ringing, is one thing; it is something else when it places more patients at greater risk. Is n ever large enough? Consider Begg's claim, in speaking of the Harvard ECMO trial, to the effect that "... the randomized portion of the trial was terminated prematurely ..." (Ware, 1989), or the even more chilling, "The real deficiency is the absence of sufficient (randomized) controls, and this can never be rectified no matter how many additional patients are treated with ECMO." Royall's criticism of the moral grounds of demonstration trials I take to be a clear rejection of Begg's demands. When he conceives of himself as engaged in constructing proofs, the demands of the investigator can be devastating for patiénts, particularly when some of the clients are slow learners.

Randomization and Probability Distributions

Third, "the process of randomization makes it possible to ascribe a probability distribution to the difference in outcome between treatment groups receiving equally effective treatments and thus to assign "significance levels" to observed differences" (Byar et al., 1976). This, I think, is the principal reason; I understand that some editors refuse to read manuscripts if the "finding" is not accompanied by a respectable significance level.

CASUISTRY

To casuistry there can be no end, both in its good and bad senses, the good because there will be no end to the bad. We are engaged in applying moral principles to particular activities, and it is clear from the literature that the person who wishes to ignore a principle contained in such documents as the Nuremburg Code or the Declaration of Helsinki will not lack for published justifications.

The arguments by Freund (1982), Byar et al. (1976) and Freedman (1987), as discussed by Royall, are new to me in this context, but similar arguments have been advanced in philosophy for centuries; the difference is, in philosophy the consequences have not been so serious. Rereading the principles with these arguments in mind, it is clear that the statements of principles are vulnerable to endless equivocation and that no wording would be invulnerable. Why is it not enough to say, "Thou shalt not experiment on human beings without their informed consent." But without even glancing at the literature we know the form of the counter arguments: Certainly one must not experiment in sense A, it will be said, but of course we may experiment in sense B. "Informed consent" will also be found to have several senses. Not only may physicians experiment without informed consent but they will be obligated to do so for the good of the greater number or some greater sensitivity and compassion for the patient. So long as vital interests are involved on both sides and the stakes remain high vigilance will be required.

Zelen's (1979) randomized consent design is, in my view, the most imaginative argument considered. Fortunately, when applied at Children's Hospital in Boston and then called to the attention of the NIH by the Boston Globe (Knox, 1989), it triggered a reprimand. The IRB at Children's Hospital was reprimanded because it was the IRB that "elected to have informed consent obtained only from the parents whose infants were randomized to receive ECMO" (Marwich, 1990). In the Rejoinder, Ware is miffed that the motives of the investigators were questioned and states that some of the comments do not "address scientific issues" (Ware, 1989). But it was Ware who used compassion for the parents to justify his actions and that was not science but casuistry, the kind, in fact, that gave it a bad name. In casuistry, questioning motives, and even pointing out that some are self-serving, is legitimate.

THE NECESSITY OF PARALLEL TRIALS

As Royall demonstrates, if personal equipoise and informed consent by the patient were preconditions, few life-threatening clinical trails would be conducted. Thus those convinced that medical progress depends on parallel trials might well fear for the future of medicine. But I do not believe that parallel trials are necessary for either the development or the perfecting of procedures such as ECMO. Begg is correct when he says, "... it is not unreasonable to suppose that there is a learning curve in the treatment of this difficult condition" (Ware, 1989). It is not unreasonable since the overall procedure as well as the surgery involve perfectible skills. Of the infants receiving ECMO, either at Michigan or Harvard, it is not unreasonable to question whether the "chances" of the first and last were comparable. It is reasonable to assume that there were important improvements in the techniques used and, if so, the statistical comparison is insensitive to them. Comparing only the living with the dead, it is insensitive to what I expect was an improvement in the quality of life of those who survived as the techniques improved. It is from a first-hand, detailed acquaintance with the procedures that confidence evolves as well as a knowledge of the direction in which improvements lie. The knowing how informs the knowing that.

Of course, statistical procedures, including adjustments, are available which can take account of learning curves as well as countless other factors, but each comes with its own set of assumptions. Moreover, the concepts do not evolve naturally and gracefully from the context; they are imposed by a theory of inference that is regarded as highly questionable by many statisticians as well as nonstatisticians.