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Adaptive Designs, Informed Consent, and the Ethics of Research

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ABSTRACT: The ethical tension in research design is often characterized as that between individual and collective ethics. While adaptive clinical trials (ACTs) are generally considered to be more sensitive to individual ethics, the concomitant loss of statistical power associated with them is often used to justify randomized clinical trials (RCTs). This paper challenges this characterization of the central ethical problem in research design. It argues that the key consideration in clinical research hinges on the process of informed consent. When the research context is such that the subject is able to provide informed consent, RCTs can be justified and may be required. However, in desperate medical situations the process of informed consent is often undermined. It is argued that in such situations ACTs are ethically required. We introduce "the principle of interchangeability" and argue that it must be satisfied if research in desperate medical situations is to be justified. *Control Clin Trials* 2001;22:203–210 © Elsevier Science Inc. 2001

KEY WORDS: *Individual ethics, collective ethics, randomized clinical trials, adaptive clinical trials, principle of interchangeability, informed consent*

INTRODUCTION

The ethical tension in clinical research has long been characterized as that between individual and collective ethics [1–3]. Thus characterized, the ethical choice is dichotomous between doing what is best for individual patients in the trial versus doing what is best for future patients who stand to benefit from knowledge gained as a result of the trial. Randomized clinical trials (RCTs) separate the pool of research subjects into distinct groups at the outset and then gather information about the responses of these groups to their assigned treatments. Although not insensitive to the needs of individual patients, the process of randomization dictates from the outset what treatment patients will get for the duration of the trial. The goal of the RCT is to acquire statistically valid information that will ensure that all patients assigned to treatment after the trial receive the most effective intervention available. Hence RCTs tend to favor collective ethics.

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Adaptive clinical trials (ACTs), on the other hand, put the priority on individual ethics. Here an ACT is defined as a design in which the allocation of treatment to each individual patient depends upon accumulated information. The objective is to treat as many patients as effectively or successfully as possible.

Although adaptive designs have been the focus of continuing research and debate in recent years, they have never become part of mainstream clinical research methodology [4–9]. Several logistical, statistical, and design issues have limited their use [10–12]. First, due to selection bias it is unlikely patients in an ACT will be balanced on relevant covariants. Second, it is often difficult if not impossible to carry out statistical tests of hypotheses at the conclusion of the trial. Also, the absence of blinding may result in response bias. Finally, ACTs are often complicated to employ, which discourages medical practitioners from implementing them. For all these reasons it has been argued that adaptive designs offer little advantage over other designs and may carry additional ethical problems in their wake [2]. RCTs remain the gold standard in clinical research [13, 14].

While not opposed to ACTs in principle, Rosenberger and Lachin [7] suggest they should be used only in narrowly defined circumstances. In particular they argue that ACTs should be used only if the disease in question is not life-threatening and the treatment under investigation has significant public health consequences. Even at that the ethical gain achieved would need to be weighed against the practicality of doing the trial. The implication seems to be that the impracticality of designing and conducting an ACT would generally outweigh any modest ethical advantage.

Contrary to Rosenberger and Lachin [7] we argue that the most appropriate use of ACTs will generally be in desperate, possibly life-threatening situations in which the risk to the individual patient is greatest. We argue that the ethical advantages of ACTs in the class of situations we identify are indeed significant, outweighing any concomitant loss in statistical significance.

On the assumption that science must serve the interests of ethics rather than the reverse, we begin by reviewing some of the moral complexity involved in the design and implementation of clinical trials. Our intent is to demonstrate that the context in which clinical trials are conducted determines, to a large extent, the moral appropriateness of the research design. While RCTs can be justified in some circumstances, they are inappropriate in others. We argue that a significant moral case can be made for the use of ACTs in situations where RCTs are morally infeasible.

INFORMED CONSENT AND THE DYNAMICS OF MORAL RESPONSIBILITY

There can be no doubt that researchers have obligations both "to safeguard the health of the people" and "to apply existing knowledge for the best possible treatment of each individual patient" [2]. Both obligations are stated in the *Declaration of Helsinki* [15]. Managing the tension between these obligations is generally accepted as the fundamental challenge in the ethical design of research giving rise to the dichotomy between "collective" and "individual" ethics. However, the *Declaration of Helsinki* recognizes no such ethical tension. Instead it states somewhat categorically that "the interests of science and society should *never* take precedence over consideration related to the well-being

of the subject" (our emphasis). There is no ethical tension here simply because the well-being of the individual patient must never be sacrificed on the altar of some perceived greater social good.

The supposed tension between individual and collective ethics arises out of the dual roles that researchers fill in the process of a clinical trial. In their primary role as researchers their objective is to gain further knowledge to safeguard public health. As clinicians, however, their objective must be to apply existing knowledge for the best possible outcome of each patient. But research participants also fulfill dual roles. As autonomous research subjects they agree to participate in scientific research that will contribute to greater general knowledge about their disease. As patients they hope that their own individual treatment will be enhanced.

Informed consent is the ethical *sine qua non* of clinical trials. In a properly designed and conducted RCT subjects are given the option to participate in a trial that includes randomization or to remain outside the trial and accept conventional medical treatment. The researcher's primary moral responsibility is to design a clinical trial that will answer a research question without exposing individual subjects to undue risks in the process. Assuming that the research question is significant, the trial is well designed, and the risks to the individual patient are justified, the tension between collective ethics and individual ethics is obviated when individual subjects give their informed consent. This is true even if the primary intent of the investigator is to compare two treatments, not to provide better overall care to the subject [16].

Reciprocity of responsibility in the sharing of information and decision making is what informed consent is all about. When fully informed subjects give their consent to participate in an RCT, they acknowledge their role as research participants and assume moral responsibility for their own autonomous choices. However the problems in attaining fully informed consent are well documented [17–22]. It is clear that in some circumstances prospective subjects are simply unable to comprehend the nature of the research and its implications for them. If informed consent is the means by which prospective participants signal their willingness to participate in a clinical trial from which they may not benefit personally, it becomes increasingly difficult to justify RCTs in situations where the likelihood of gaining a fully informed consent is minimal.

Now the class of cases for which Rosenberger and Lachin [7] recommend the use of ACTs, namely when the disease is not life-threatening and the treatment under investigation has significant public health consequences, are exactly the kind of situations in which the consent process would justify the use of RCTs. In such generally innocuous circumstances subjects are more likely to appreciate the dual roles of the researcher and to understand that the clinician responsible for their care is also a researcher conducting a clinical trial. Subjects are also more likely to comprehend the nature of the research proposed and less likely to be confused in their decision-making processes by the momentous affects of illness, the expectation of a possible miracle cure, and concomitant emotional states.

Contrary to Rosenberger and Lachin [7] we argue that the use of ACTs are ethically more appropriate in desperate medical situations. We describe desperate medical situations generally as those in which the patient is suffering from a serious, acute, and potentially debilitating or terminal illness if effective

treatment is not provided. As the relative risk to the individual subject increases it becomes increasingly difficult to justify the use of RCTs on ethical grounds. The reasons for this are twofold, the first pertaining to the matter of informed consent, the second to the clinician's duty of beneficence.

Conditions that undermine the patient's autonomous capacity to make an informed decision are referred to in the ethics literature [23] as "controlling influences." Controlling influences are of especial concern in the kind of desperate medical situations we are considering here. In such situations the prospective subject's capacity to appreciate the clinician's dual roles as both researcher and clinician can be largely negated. Patients will often have unrealistic expectations of what any proposed intervention might offer [24]. They will understandably expect that their physicians will act first as clinicians whose primary concern is their physical well-being and care [25]. The physician's dual role as researcher will be far from view in such circumstances, and from the patient's point of view will often appear irrelevant to the clinical decision that must be made. Hence the subject's capacity to provide a fully informed consent to any proposed research might be almost entirely compromised.

The problem is graphically illustrated in a poststudy analysis of parents whose critically ill babies were randomized to different treatment arms in the British Extracorporeal Membrane Oxygenation (ECMO) study [26]. Parents presented with a critically ill child had little time to absorb information about the proposed trial or to make a decision with which they were comfortable. Many had little comprehension of the purpose of randomization. Some believed the process was designed to relieve their physician of the personal responsibility to make a difficult clinical choice about which treatment their desperately ill baby was to receive. Others did not even understand until sometime later that their baby had been enrolled in a clinical trial. Inasmuch as the process of informed consent serves as the ethical justification for RCTs, the low probability of achieving informed consent militates against their use in such critical situations.

Now it is clear that not every patient in a desperate medical situation will necessarily be unable to provide informed consent. Some may comprehend the nature of their condition, the risks involved with various proposed treatments, and the possibility that they may receive an inferior treatment if they agree to be enrolled in an RCT. This is where the second mitigating reason against the use of RCTs comes to the fore, and it pertains to the physician's duty of beneficence. We would argue that in desperate medical situations the duty of beneficence dictates that the physician's role as clinician must take precedence over that of research scientist. Hence every effort must be made to provide the most effective treatment given current information.

Federal regulations in the United States [27] and policy provisions in Canada [28] allow for the use of unproven therapies in emergency situations when subjects are unable to provide consent. A key requirement of such provisions is that the physician in charge judges that the physical well-being of the individual patient necessitates immediate intervention. This focus on the individual patient thus precludes randomization. Hence the strategy adopted in such circumstances is myopic. By definition, a myopic strategy always selects the treatment with the higher expected immediate payoff. In such situations the permitted interventions would be better described as "therapeutic intervention

with an unproven treatment" rather than "research" per se. Be that as it may, such regulatory provisions presuppose that the patient is physically incapable of providing consent. We argue that a similar provision is necessary when patients are emotionally incapable of providing consent [21] due to the dire medical circumstances in which they find themselves.

Aside from the special case that can be made for access to new interventions on compassionate grounds, unproven treatments should be restricted to those in clinical trials [25]. Hence any proposed research in such circumstances must be designed to maximize the subject's opportunity to receive the best available treatment given current information. This is exactly what ACTs are designed to do. While the physical well-being of the patient/subject is the priority, the use of adaptive designs in these situations ensures that research goals can still be pursued.

Summing up, the ethical justification for RCTs is found in the process of informed consent. Hence, RCTs are appropriate when informed consent can be obtained. Informed consent is generally not obtainable in desperate medical situations. It follows that the moral justification for RCTs in such circumstances is compromised. Nevertheless, the moral imperative to provide the best available treatment for individual patients requires that ongoing research should be conducted even with patients in dire situations who are not able to provide full and informed consent. In such circumstances the researcher must assume a higher duty of care for the subject. In situations where ongoing research is required the design of the research must minimize the risk to individual subjects, irrespective of the greater collective good. ACTs are designed for this purpose. Hence ACTs are ethically justified in desperate medical situations and may be morally required.

THE PRINCIPLE OF INTERCHANGEABILITY

Now that we have established that the interests of the individual subject must always guide decisions about the appropriate design of a clinical trial, we propose that an appropriate design for desperate medical situations must satisfy what we call the "principle of interchangeability."

Suppose there are n patients to be treated both in and after the trial, and each patient is treated by one and only one of two treatments. We say that a design satisfies the principle of interchangeability if any two of these n patients are ethically interchangeable. That is, at the point of enrollment in a clinical trial the intent must be to provide the best treatment available to each patient given current information. We stipulate that the principle of interchangeability applies primarily in dire medical circumstances because it is in such situations that the patient's capacity to provide an informed consent is most likely to be compromised.

In desperate situations subjects often fail to understand the nature or rationale for the research and hence are incapable of providing an informed consent. Such subjects do not so much choose to enroll, but are rather chosen and then enrolled. The researcher must then assume a greater degree of responsibility for the well-being of the patients and act always in their patients' best clinical interest. Designing a study that is ethically optimal thus involves a sequential decision problem in the face of uncertainty and is not of the classical

inference type. In such cases the guiding goal in the choice of research methodology and study design must be to satisfy the principle of interchangeability. Thus each patient's fate is determined not by the particular design of the trial but rather by the chance and timing of getting the disease.

Neither fixed-size RCTs nor sequential clinical trials (SCTs) satisfy the principle of interchangeability. In an RCT a fixed sample size n is determined based on considerations of significance and power. Patients in the trial are in turn randomized. In an SCT n is random and minimized but simple randomization is again used in the trial. Patients in an SCT are randomized to the treatments as long as there is "genuine doubt" about the efficacy of the treatments. Patients after the trial receive better treatment based upon the "near certain" conclusion of the trial. It is worth noting that the knowledge and scale of reliability of evidence between "genuine doubt" and "near certainty" is continuous. The last patient enrolled in the trial has only a 50/50 chance of receiving the better treatment. However, the first patient treated after the trial has a much higher chance of receiving the better treatment even though the information available in both cases is almost identical. Thus the two patients are not ethically interchangeable.

The principle of interchangeability is satisfied when we maximize the expected total responses from all patients to be treated. If the responses are immediate and dichotomous such as in the ECMO trial, this will result in the maximization of the expected total number of successfully treated patients. If responses are delayed such as in survival trials for cancer or AIDS, the expected total patient survival time after treatment will be maximized. Such an optimization problem is essentially a bandit problem with immediate [29] or delayed [30] responses. An optimal strategy is characterized by the dynamic programming equation that states that under current information the current patient is offered the best treatment available given that all future patients are treated optimally. Such a recursive property of the optimality equation indicates that the objective of optimization satisfies the principle of interchangeability.

By means of simulation Berry and Eick [31] have compared the performance of four adaptive designs with balanced randomization. Although adaptive designs are more difficult to use, they suggest that ACTs may be more appropriate when the majority of patients are recruited in the trial. Elsewhere [32] we have made a general comparison between the bandit model and randomization and show that under certain conditions the total regret of successes lost is smaller with an adaptive design. Other simulation studies demonstrate that adaptive designs perform better than sequential trials and simple randomization (please refer to our earlier work [32] for a summary of these results).

The fundamental characteristic of an optimal strategy is that it provides a compromise between gathering information about the effectiveness of available treatments to provide better informed decisions in the future, and maximizing total combined responses for current and all future patients [31]. By nature such a strategy is adaptive. Randomization aims only to gather information and thus ignores immediate responses. On the other hand, a myopic strategy that always selects the treatment with the higher immediate payoff focuses on immediate responses and ignores information gathering. RCTs and myopic strategies represent two extremes and are not optimal in general [31].

CONCLUSION

Although we have argued that adaptive designs perform better ethically than randomization in certain clinical situations, we expect continued resistance to the use of ACTs even in these restricted circumstances. Our hope is that by identifying a narrow class of cases in which ACTs are clearly superior on ethical grounds we will contribute to a softening of this bias in some quarters.

There are, of course, ongoing theoretical obstacles to overcome. It remains difficult even in simple situations to find an optimal or nearly optimal adaptive design that is practically feasible. There is also a need to develop appropriate statistical methods for analyzing results obtained from such designs. Finally, ideological and practical barriers to the use of ACTs come together in the competitive grant application process. Researchers may hesitate to propose an innovative design if they fear it may not be readily understood or accepted by those who review their project. Hence, there is a need to further educate the research community on the complex and often momentous ethical issues involved in the choice of a research design. Overcoming such resistance will require moral courage on the part of investigators, granting agencies, and journal editors alike [33] if the research community is to fulfill its moral mandate.

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