Steven Joffe Robert D. Truog

24

Equipoise and Randomization

Most observers believe that randomized controlled trials (RCTs) offer the highest standard of evidence about the safety and efficacy of proposed new treatments.[1] When a new therapy's benefits are dramatic, nonrandomized studies may suffice to show its advantages. However, therapeutic advances more often involve small to moderate incremental benefits. Such benefits may be of substantial public health importance, particularly for common conditions.[2] Without the ability to conduct RCTs, efforts to evaluate such benefits are fraught with potential for error.

However, RCTs raise ethical challenges. In particular, randomizing patients to receive the experimental therapy, or a conventional therapy, or perhaps placebo, creates a dilemma. Clinicians are ethically required to offer patients the best available therapy. But researchers may propose to offer some participants in the trial an intervention that does not meet this "best available" standard.

Randomization is controversial in part because it draws attention to the uneasy coexistence of experimentation and therapy that exists in most clinical research. Notions of equipoise, which invoke some form of indifference between the interventions offered in a trial, have played a central role in efforts to reconcile the tensions between the roles of clinician and experimenter inherent in RCTs, and have found a place in the U.S. Department of Health and Human Services guidance regarding research design.[3]

However, equipoise is not universally accepted as the solution to the problems raised by RCTs. Definitions of equipoise vary, many authors doubt that it succeeds in reconciling the obligations of science and care, and more radically, some recent critics deny any need for such reconciliation. The epistemological assumptions underlying the notion of equipoise are also debated.[4] Finally, even if the argument for equipoise is correct, it ignores many of the ethical questions that RCTs pose.

In what follows, we outline the rationale for and methodological basis of RCTs, review the history of equipoise, discuss the different conceptions and critiques of equipoise, attempt to situate the challenges associated with RCTs within a systematic framework for ethical research, and suggest scientific and policy implications of these challenges. We also review the relevant empirical data in order to tie normative discussions of equipoise and other ethical concerns to the real-world practice of RCTs.

Before beginning, another word about terminology is in order. Because there are numerous competing notions of equipoise, and the word itself is so unfamiliar in ordinary discourse, in this chapter we will favor a neutral term—*indifference*—unless we are discussing specific conceptions of equipoise advocated by particular authors.

Randomized Trials: Core Conception and Methodological Rationale

All clinical research that aims to inform choices about prophylactic, diagnostic, or therapeutic interventions involves comparing the relative merits of two or more possibilities. Consider a hypothetical single-arm study that appears to show improved outcomes among individuals exposed to a new intervention, compared with outcomes among a historical control group of patients exposed to a standard intervention. There are at least five potential explanations for this apparent benefit. It may result from between-group differences in demographic or other characteristics independently

associated with the outcome under study—that is, from confounding due to selection bias. For example, individuals receiving the new intervention may be younger or healthier than the historical controls. Or, the benefit may result from differences in investigators' interactions with or observations of subjects—that is, from better supportive care, more intensive diagnostic testing, or reduced loss to follow-up. The improvement could be a placebo effect related to expectations about the new therapy. It might simply be due to chance. Finally, it may represent a true difference in treatment efficacy. These alternative explanations for the observed data must be considered whether or not results favor one of the treatments.

RCTs employ three or more devices to minimize the likelihood of false-positive and false-negative errors (see Table 24.1). First, they use concurrent controls, thereby permitting direct comparison between groups[5] and eliminating confounding by temporal trends. Second, they divide participants into groups using some method of random allocation, thereby increasing the likelihood that the groups will be comparable at baseline.[6] This is important because, though methods to adjust for known covariates are available, these methods are both imperfect and unable to control for unmeasured or unrecognized confounding variables. Third, RCTs employ statistical tests and sample size calculations to quantify and control the chances of false-positive and false-negative results. In addition, many trials conceal treatment allocation from subjects and/or investigators (a technique known as single- or double-blinding) to reduce the chance that investigators or subjects will tilt the trial by unconsciously favoring one group over the other. Finally, some trials use placebos to facilitate blinding. Such rigorous methodology helps maximize the scientific validity that is among the primary requirements for ethical research.[7]

Of these five error-minimizing devices, use of concurrent controls and statistical tests present no special ethical problems, though the choice of statistical approaches may have ethical implications,[8] as discussed below. Randomization, however, has been debated for at least 40 years. Blinding, though less scrutinized, also raises ethical challenges. Special concerns related to placebos arise when control participants are asked to forgo therapy that is otherwise available[5,9–12] (see Chapter 25).

Table 24.1
Error-Minimizing Features of Randomized Trials

Feature	*Purpose*
Concurrent controls	• Eliminate between-group differences due to temporal trends • Enable direct comparisons
Randomization	• Reduce likelihood that groups will differ at study entry
Statistical tests, sample size calculations	• Control chances of false-positive and false-negative results
Blinding*	• Reduce likelihood that investigators will interact with or observe study participants in ways that differ systematically between groups • Reduce chance that participants will behave or report symptoms in ways that differ systematically between groups • Distinguish physiologic from placebo effects
Placebo administration**	• Facilitate blinding when interventions differ in observable ways between groups

*Not all randomized trials involve blinding or placebo controls.

**In a subset of trials involving placebos, participants in the control arm may be asked to forgo treatment that is available in the context of standard care.

There are two general statistical approaches to designing and analyzing RCTs. The most prevalent method, called frequentist, begins with a null hypothesis: that there is no difference in outcome between Treatment A and Treatment B. Before the trial begins, investigators define a probability threshold, called an alpha error, beyond which they will reject the null hypothesis as statistically improbable. The experiment proceeds, and the data are used to calculate the conditional probability, assuming the null hypothesis is true, of "observing a result equal to or more extreme than what was actually observed."[13] If this conditional probability (or *P* value) is smaller than the predefined alpha error, the null hypothesis is rejected and the alternative hypothesis—that there is a difference in outcome between Treatment A and Treatment B—is accepted by default. It is critical to note the common misconception that the *P* value describes the probability that the observed difference reflects a false positive. The *P* value represents the probability of the observed data given no true difference, not—as often assumed—the probability of no true difference given the observed data.[14]

An alternative analytic approach, called Bayesian, eschews null hypotheses and hypothesis tests. Instead, it starts with an assumption (which may be either subjective or evidence-based) about the true difference in outcome between Treatment A and Treatment B. This assumption takes the form of a prior probability distribution. The experiment is conducted, and the data are used to calculate a measure of the weight of the evidence (known as the Bayes factor or likelihood ratio). This measure is then combined mathematically with the prior distribution to generate a posterior probability distribution. The posterior distribution represents an updated estimate, taking into account information learned from the experiment, of the true difference between A and B.[15–17]

Historical Perspective

Most discussions of the ethics of RCTs have revolved around the possibility of conflict between research and treatment. The felt need to defend RCTs as consistent with physicians' therapeutic obligations was evident by 1949, when Walker and Barnwell cited the lack of "genuine ignorance or doubt that the drug in question has any therapeutic value" to justify their decision against randomizing in an early U.S. Veterans Administration study of streptomycin for pulmonary tuberculosis.[18] Fisher, who developed the statistical theory underlying randomization, wrote in 1958 that RCTs are acceptable "so long as no body of medical opinion can say with confidence that one [new drug] is better than the other." (Interestingly, in the same article he criticized the mounting but nonrandomized evidence of an association between cigarette smoking and lung cancer as insufficient to prove causation.)[19] Hill, who helped design the earliest published RCT, the British streptomycin trial, wrote in 1963: "Only if, in his state of ignorance, [the doctor] believes the treatment given to be a matter of indifference can he accept a random distribution of the patients to the different groups."[20] Importantly, Hill did not

invoke indifference in defending the decision to randomize tuberculosis patients to streptomycin versus observation. Rather, because insufficient streptomycin was available to treat all eligible patients, he viewed a random lottery as a fair way to ration the drug while facilitating collection of valuable data[21] (see Chapter 4).

Charles Fried's 1974 treatise systematized the theoretical case for the indifference requirement, pointed to the clinician-investigator at the bedside as the primary locus of the moral dilemma, and suggested ways to resolve or lessen the quandary, including emphasis on informed consent and greater openness to nonrandomized designs.[22] Fried's essay opened the modern history of the notion of equipoise.

The Ethics of Randomization

Ethical concerns about randomization, the most striking feature of RCTs, focus on two related but separable aspects of trial conduct. First, some critics object that participants must forgo their right to "personal care."[22,23] Put differently, physicians have a duty, grounded in the fiduciary nature of the patient-doctor relationship, to make individualized treatment recommendations in the context of patients' particular values and circumstances. When physicians also act as investigators, randomization seems to force them to violate this duty. Second, commentators raise the more consequentialist concern that randomization may require assignment of some participants to therapy that is likely to be inferior, even though the preliminary evidence supporting that judgment falls short of conventional standards of methodological rigor. Emerging data during the course of a trial that appear to favor either treatment exacerbate these problems. Reviews of ethical aspects of RCTs are available.[24,25]

The most common defense of RCTs is to claim a state of indifference between the two treatments—that is, that they are "an equal bet in prospect."[25] Many versions of this requirement have been proposed. Mostly they vary along two dimensions—whether indifference is for physician-investigators or patient-subjects to determine, and whether it should operate at the individual or community level. (Table 24.2 attempts to clarify the nomenclature.) Although these views of indifference vary, they share the intuition that it is ethical to conduct a trial or enroll a patient when there are no strong reasons to favor one treatment over the other. Thus, under indifference, clinician-investigators can fulfill their commitments to personal care while avoiding charges of giving patients predictably inferior therapy.

Table 24.2
Four Conceptions of Equipoise

	Clinician-Investigator	*Patient-Subject*
Individual*	Individual equipoise**	Patient equipoise
Community	Clinical equipoise†	Community equipoise

*The *uncertainty principle* invokes individual preferences among both clinician-investigators and patient-subjects.

**Sometimes called *theoretical equipoise* or *Fried's equipoise.*

†To complicate matters, Gifford has used *community equipoise* to refer to Freedman's notion of clinical equipoise.[30]

Fried's view, which others have termed *individual* or *theoretical* equipoise, established the benchmark for subsequent authors.[22] (Table 24.3 catalogs the key positions in the debate.) Concerned mainly about randomization's challenge to personal care, Fried held that it is ethically problematic for a physician who favors either treatment to offer enrollment in a trial if his or her preferred treatment is available outside the trial. Furthermore, personal care requires that physicians consider patients as individuals with unique values and circumstances, not as generic exemplars of a given condition. Fried contended that when physicians take such individual factors into account, instances of genuine indifference between treatments for particular patients will be rare. For Fried, physicians' fiduciary obligations require that they share their beliefs with their patients and recommend their preferred treatment when it is available. Variations of this position continue to appear.[23,25–33]

The difficulties of conducting RCTs within the constraints of the requirement that individual physicians be indifferent are obvious. Physicians will usually have at least weak treatment preferences, which would impose moral obligations at a minimum to share their preferences with patients and perhaps even to recommend against or decline involvement with the trial. Also, the physicians who conduct a trial are often the same individuals who have led the clinical development of the intervention; they are naturally motivated because they believe the intervention may be superior to standard therapy. Demanding that those who developed the experimental treatment be indifferent about its merits in comparison with standard therapy might seem an unreasonable constraint. Furthermore, even if physicians are indifferent at the start of the trial, they will often develop preferences as it progresses. And they cannot ethically agree to the withholding of interim results to avoid this problem, because doing so violates their obligations of advocacy and fidelity. Though Fried did not wish to create an insurmountable barrier to RCTs, it is difficult to imagine beginning a trial or bringing it to completion in the moral universe he describes. As Hellman and Hellman have argued, "even if randomized clinical trials were much better than any alternative . . . the ethical dilemmas they present may put their use at variance with the primary obligations of the physician. . . . We must develop and use alternative methods for acquiring clinical knowledge."[23]

Before discussing responses to Fried, an aside about the problem of personal care is in order. Because randomization spotlights the fact of experimentation, it sometimes seems like a methodological streetlamp under which we search for our lost ethical keys. In fact, virtually all intervention studies—not just RCTs—challenge obligations of personal care.[34] Consider a single-arm trial that has enrolled 18 subjects, none of whom responded to the experimental agent.[35] The protocol specifies closing the trial and declaring the drug ineffective if none of the first 19 subjects responds. Is it ethical to enroll the next eligible patient if alternatives are available? Or consider the more pedestrian example of a chemotherapy research protocol that specifies a white blood cell (WBC) count of 1500/uL before beginning each cycle. Adherence to the protocol would require that the subject who arrives in clinic with a WBC of 1450/uL be sent home, even if proceeding with therapy would be clinically reasonable. Thus, if the argument from personal care holds, RCTs are hardly unique in presenting ethical challenges to the conduct of clinical research.

An alternative view holds that standards within the clinical community, rather than individual physicians' inclinations,

Table 24.3
Equipoise and Other Responses to the Problem of Treatment Preferences in Randomized Trials

Position	*Core Argument*	*Representative Citations*
Arguments From Equipoise		
Individual equipoise	Physicians must view the treatments offered in an RCT as "equal bets in prospect" in order to enroll patients. Some advocates of this position argue that this condition is unlikely ever to be met and would therefore discard RCTs on ethical grounds.	Fried[22]; Hellman & Hellman[23]; Markman[31]; Royall[28]; Hellman[26]; Gifford[30]; Edwards et al.[25]
Equipoise among expert clinicians	An RCT is ethical if there is uncertainty or disagreement within the expert clinical community about the relative merits of the two therapies.	Freedman[36] ; Miller & Weijer[40]; Weijer et al.[188]; Weijer[37]
Standards of evidence	An RCT is ethical if there is no scientifically validated reason to favor either treatment in the trial.	Levine[1]
Patient equipoise and informed consent	Patients, rather than clinicians, must be indifferent among the various treatment options when enrolling in a trial. Closely related to the view that the patient-subject's informed consent, not the objective state of knowledge or physicians' beliefs, is the primary ethical precondition for RCT participation.	Angell[41]; Marquis[42]; Lilford[43]; Ashcroft[44]; Veatch[45]; Menikoff[46]; Gifford[39]
Community equipoise	The locus of uncertainty or disagreement includes not just expert clinicians, but also patients and their representatives.	Karlawish & Lantos[47]
Uncertainty	The ethical precondition for enrolling a patient in a trial is a state of uncertainty—not necessarily of equal prior probabilities—on the part of clinician and patient about which of two or more treatments is preferred. Combines features of individual and patient equipoise.	Peto et al.[2]; Peto & Baigent[49]; Sackett[48]; Enkin[51]
Alternatives to Equipoise		
Altruism	Patients' desires to assist in learning something of value justifies their participation in RCTs.	Meier[53]; Royall[54]
Social contract	By virtue of the benefits they receive from prior research, persons have correlative obligations to participate in trials, even at some limited cost to themselves.	Wikler[57]; Gifford[56]
Consequentialism	Experimentation in RCTs cannot be reconciled with patients' rights to optimum personal care. Only an ethic that looks to the greatest good for the greatest number can justify such trials.	Marquis[62]
Debate rests on false premises	Notions of equipoise are based on a misconception about the relationship between research and therapy in RCTs. It ought to be discarded in favor of a conception that is specific to research.	Miller & Brody[66]

should determine whether RCT participation is acceptable. Freedman's 1987 description of *clinical equipoise,* which took this approach, was perhaps the most influential response to Fried's challenge.[36] Freedman argued that physicians' knowledge—and therefore the scope of their therapeutic obligations—is collective and professional rather than individual in nature. If so, he argued, clinicians who offer participation in RCTs are behaving ethically so long as there exists "an honest, professional disagreement among expert clinicians about the preferred treatment."[36] In Freedman's view, absent professional consensus, a clinician's hunches or preferences pose no moral barrier to trial recruitment.

In a recent extension of Freedman's work, Weijer noted that clinical research often includes some procedures "administered with therapeutic intent and others that answer the research question" (presumably, the experimental treatment under study in an RCT is among the procedures "administered with therapeutic intent").[37,38] He argued that the equipoise requirement applies specifically to these "therapeutic" procedures. Based on the work of the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, he advocated a "components approach" in which each element of a trial would be judged according to standards appropriate to its intent. Thus, a biopsy undertaken exclusively to address a scientific hypothesis would be acceptable if risks were minimized and were reasonable in relation to the knowledge gained (i.e., a research-specific evaluation standard). In contrast, administration of a promising new agent with therapeutic expectations in the context of a randomized trial would be acceptable if it met Freedman's test of clinical equipoise.

Levine has argued that a trial is ethical if "there is no scientifically validated reason to predict that Therapy A will be superior to Therapy B. Further, there must be no Therapy C known to be superior to either A or B."[1] This position bears a fundamental kinship with Freedman's statement of clinical equipoise, because what constitutes a "scientifically validated reason" depends on community standards.

Although individual and clinical equipoise differ in a number of ways,[39] the contrast in moral locus of decision making is among the most salient. Recently, Miller and Weijer have suggested that the choice between equipoise at the individual or clinical community level represents a false dilemma; both may be ethically necessary.[40] They argue that clinical equipoise is a social condition that legitimates the initiation or continuation of a trial, whereas individual equipoise justifies the clinician-investigator's decision to offer or recommend trial enrollment to a patient. In practice, sorting through these conditions is often difficult. In Box 24.1, we describe a case in which, to the clinicians involved, neither level of equipoise seemed sufficient by itself to justify a trial.

A third important conception of the indifference requirement, hinted at by Fried and developed more fully by others, emphasizes the views of the patient-subject rather than the clinician-investigator.[41–46] The acceptability of trial participation depends crucially on how the subject values the various probabilities and outcomes associated with trial enrollment, because it is the subject who will experience the consequences. Thus the subject, not the clinician-investigator, must be reasonably indifferent between the treatments offered in the trial.

Two features of the patient indifference perspective bear mention. First, because only the subject can provide ethical justification for trial participation, the argument rests entirely on valid informed consent. Proponents have not considered this principle's implications for RCTs, such as trials involving young children or occurring in emergency situations, in which autonomous consent is not possible. Second, this view highlights the need to think broadly about what endpoints we have in mind when we speak of being indifferent between two treatments. Clinician-investigators might be indifferent with respect to the trial's "hard" endpoints—mortality or major morbidity—but prospective trial participants are likely to consider factors such as quality of life and practical burdens as well.[39] Mastectomy and local resection with radiation may result in similar survival for most women with limited-stage breast cancer, but many women will have strong preferences depending on how they value such factors as disfigurement and the possibility of local recurrence. Lilford and Jackson have shown how one might model such tradeoffs to arrive at "effective" equipoise.[27]

Box 24.1
A Case Involving Different Conceptions of Equipoise

In 2004, clinicians at Boston Children's Hospital discussed an RCT involving assignment of critically ill children to groups that would receive red blood cell transfusions at threshold hematocrits of either 21% or 27%. Though the current local practice was to transfuse at about 21%, no data existed to support this cutoff and practices varied across institutions. On the basis of this broader disagreement, a few clinicians argued for an ethical obligation to support the trial in order to help resolve this important question. Most, however, insisted that unless there was personal uncertainty, or at least disagreement within the local group, it would not be ethical to enroll patients. Thus three versions of the equipoise position were in play in this debate: (1) clinical equipoise, as described by Freedman; (2) equipoise within the *local* expert community; and (3) individual equipoise, as described by Fried.

Just as Freedman highlighted the role that lack of consensus within the expert clinical community plays in legitimizing an RCT, others have emphasized the importance of disagreement or indifference within the patient community.[47] According to this position, for a trial to be ethical, the community that must be in equipoise includes representatives of those who would be eligible for the trial. As with clinicians, individual patients and communities of patients may have complementary roles in legitimizing a trial.

A final group of authors argues that uncertainty, not equipoise, best articulates the ethical basis for RCTs.[2,48–51] According to Peto and Baigent,

> A patient can be entered if, and only if, the responsible clinician is substantially uncertain which of the trial treatments would be most appropriate for that particular patient. A patient should not be entered if the responsible clinician or the patient are for any medical or non-medical reasons reasonably certain that one of the treatments that might be allocated would be inappropriate for this particular individual (in comparison with either no treatment or some other treatment that could be offered to the patient in or outside the trial).[49]

At first blush, it is not entirely evident how this "uncertainty principle" differs from some conceptions of equipoise. (Compare it with Levine's formulation above.) One important difference, however, is that, against Freedman, advocates of the uncertainty principle wish to place the moral onus back on the individual physician and patient who must decide about trial participation, rather than on the community of experts.[52] Proponents of the uncertainty principle also reject the "etymological connotation of an equal balance between . . . the alternatives to be tested" inherent in the word *equipoise*.[51] They insist instead that, for an RCT to be ethical, the metaphorical "confidence intervals" around one's hunches of benefit must include the possibility of no effect or of harm. This is a much less fragile conception than the individual equipoise described by Fried.[51] Nevertheless, the uncertainty principle qualifies rather than radically revises the notion of equipoise.

Reconciling Clinical and Scientific Obligations in Randomized Trials

The justifications for RCTs reviewed above all invoke some version of the indifference requirement. However, some authors suggest that indifference may be neither necessary nor sufficient to justify trials. These commentators offer frameworks that—either alone or in combination with arguments from indifference—might provide alternative ethical foundations for RCTs.

One defense of RCTs appeals to patients' altruism to justify a limited loss of benefit associated with the possibility of randomization to inferior therapy.[53,54] In Meier's words, "most of us would be quite willing to forgo a modest expected gain in the general interest of learning something of value."[53] Like the patient indifference approach, invoking altruism as a defense of trials rests heavily on valid consent and raises problems for trials involving those who lack capacity to consent.[54] It is also amenable to empirical investigation of participants' reasons for enrolling in trials.[55]

A second justification appeals to the notion of social contract. Gifford, in a promising account, explored such an approach to

reconciling patients' self-interests and right to personal care with efforts to advance the common good. He suggested that "morality and political institutions are conceptualized as . . . cooperative ventures for mutual advantage, and each person can see that it is in his interest to have such an institution."[56] RCTs might be among the institutions that invite justification in this way. Wikler took a similar line, asking us to imagine a choice of "citizenship in one of two societies. In the first, doctors always give their patients the best care they can, whereas in the second, patients are sometimes slighted in the interest of medical progress. The state of the art of medicine, however, is more advanced in the second than in the first."[57] Many people, he argued, would choose citizenship in the second society. Several authors have considered the broader but related question, based in considerations of fair play and free ridership, of whether persons have prima facie obligations to participate in clinical research.[58–61]

A third option invokes the consequentialist notion that the social benefits of trials outweigh their costs to individuals. For example, Marquis reluctantly suggested that an ethics of conscription, defended on consequentialist grounds, might be necessary to justify the conduct of these trials.[62] Others have discussed the broader role of consequentialism in the ethics of medical research.[50,63–65]

Finally, in 2003 Franklin Miller and Howard Brody posed a radical challenge to the central question underlying the equipoise debate. They argued that concerns about equipoise derive from the widely held but (they believe) incoherent "similarity position," which holds that "the ethics of clinical trials rest on the same moral considerations that underlie the ethics of clinical medicine."[66] In their view, this position contradicts the fundamental assumption of research ethics, as articulated in the Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: "The ethics of clinical trials must start with the realization that medical research and medical treatment are two distinct forms of activity, governed by different ethical principles"[67] (see Chapter 14). According to the Belmont Report, clinical care involves activities "that are designed solely to enhance the well being of an individual patient or client and that have a reasonable expectation of success," whereas research denotes "an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge."[67] To suggest that equipoise can unite the ethical conditions for these two activities represents a category mistake.

Rather than ask whether an RCT satisfies clinical equipoise, Miller and Brody would assess it against principles appropriate to the evaluation of research.[7] The key question is not, as proponents of clinical equipoise argue, how the interventions offered in a trial compare with competent medical practice. Rather, investigators and reviewers must ensure that the study does not exploit subjects. This condition requires that the question is worth asking, the methods are sufficient to answer the question at hand, the risk-benefit ratio—integrating risks and benefits to individual participants with benefits to the community of future patients—is favorable, and subjects give valid informed consent. The most important implication of this view is that, to estimate the risk-benefit ratio of any study involving human subjects, one must incorporate considerations of societal benefit.[67,68] The confusion at the heart of the various arguments from indifference lies in their denial that this is as true for RCTs as it is for other research designs.

Miller and Brody's framework is particularly helpful for analyzing and justifying studies, such as certain placebo trials, that offer some subjects less expectation of benefit than they might receive under standard care. However, conceptual questions and practical problems remain, and though the authors attempt to address these, it is not clear how their proposal will play out in the clinic.[69] For example, can we realistically ask individuals to trade the status of patient for that of subject when they enter a trial, or must we articulate a coherent vision of them simultaneously as patients and subjects? If patients, particularly those with serious illnesses, come to physicians with expectations of receiving optimum therapy, how will the explicit denial of therapeutic obligations affect subject recruitment and trust in research?[70,71] On what normative grounds do we proceed when studying persons who cannot provide informed consent, such as children or patients involved in emergency exception research? Given these considerations, Weijer and Paul Miller counter that the components approach discussed above, which assesses research and therapeutic elements of a trial according to different criteria, better reflects the insights of the National Commission.[72]

Practical Responses to the Problem of Reconciling Clinical and Scientific Obligations

As noted previously, various formulations of the indifference requirement offer potential solutions both to the problem of personal care and to the concern that some patients might be randomized to predictably inferior therapy. Conceptual debates focus mainly on the deontological issues related to personal care, and secondarily on the more consequentialist problem of assignment to inferior therapy. In contrast, discussions about practical ways to ameliorate these problems seek primarily to minimize the number of subjects who receive inferior therapy.

A historically important suggestion for ensuring indifference is to randomize beginning with the first person exposed to a drug.[73] This argument recognizes that preliminary, usually uncontrolled data available prior to the first RCT tend to disturb indifference sufficiently to make subsequent studies ethically and logistically challenging. Although theoretically plausible, in the real world there are valid reasons that new therapies do not reach the point of evaluation in an RCT until after they have been evaluated (sometimes extensively) in early-phase research.[74] By this time, evidence for their efficacy already exists. Nor does this suggestion resolve the practical problem caused by trends that emerge during the course of the study. Knowledge of such trends could lead to treatment preferences among clinician-investigators and potential subjects that could threaten study completion.

The practical challenge posed by interim data has led to the standard but controversial practice of withholding the information from investigators, referring physicians, and enrolled and potential subjects.[75] Veatch has written that withholding such information may sometimes be acceptable when subjects are aware of and consent to it in advance, but that "where the information really is crucial such consent to ignorance will be morally unacceptable."[76] Levine held that it is acceptable to "ask the subject to consent to . . . acceptance of the standards of proof agreed upon within the community of professionals" regarding emerging efficacy trends.[1] Freedman suggested that clinical equipoise alleviates the ethical difficulties caused by emerging trends, because until

the evidence is sufficient to convince the expert clinical community, clinical equipoise is maintained.[36] He further argued that, if clinical equipoise suffices to justify a trial, then withholding interim data should be unnecessary. (The routine concealment of such data suggests that, though investigators may endorse the abstract notion of clinical equipoise, they are unwilling to bet their own trials on it.) Finally, Lilford et al. argued against the withholding of interim results.[75]

In concert with the practice of withholding interim results, data monitoring committees (DMCs)—also known as data safety and monitoring boards (DSMBs)—are widely used to deal with the problem of emerging trends[50] (see Chapter 53). DMCs, which should be independent of the sponsor and principal investigator, review interim data regarding toxicity and efficacy. They are charged with deciding when the accumulated evidence justifies closing the trial. Ideally, the decision to close a trial respects protocol-specified stopping guidelines that function to preserve both the scientific validity and the ethical integrity of the trial. DMCs may close trials early for several reasons, including poor accrual or other logistical problems, unanticipated toxicity in one or both arms, lack of an emerging difference between arms (futility), or unexpectedly strong evidence for a difference between arms (efficacy). In the context of the present discussion, their major role is to close a trial when the data are sufficient to answer the research question. The possibility of stopping early minimizes the number of subjects assigned to the less effective treatment, while permitting the better therapy to be offered sooner and to larger numbers of patients outside the trial. Decisions about early stopping, which are the subject of considerable statistical discussion, are among the most ethically charged in all of clinical research[53,77–79] and will always generate controversy.[80,81] In our view, they require greater attention from the research ethics community than they have heretofore received.

Decisions about when to stop an individual trial are obviously connected to judgments about when to declare uncertainty resolved and a particular line of inquiry closed. This critical issue has received only limited attention in the research ethics literature.[82] Despite the concerns that they raise,[1] it has been customary to conduct confirmatory trials in many circumstances. Guidance from the U.S. Food and Drug Administration (FDA) states that "the usual requirement for more than one adequate and well-controlled investigation reflects the need for *independent substantiation* of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness."[83] Parmar has described Bayesian methods for making explicit decisions about when residual uncertainty justifies confirmatory trials.[84]

A second strategy for minimizing the number of subjects exposed to the inferior intervention involves unbalanced randomization, with a ratio favoring the preferred arm.[85,86] A more complicated approach has been called *adaptive randomization,* or "play-the-winner."[86,87] In this design, subjects are initially assigned to the experimental or standard treatment in a fixed ratio. However, as the data begin to favor one treatment or the other, the allocation ratio tilts toward the preferred arm. When there are large differences between treatments and results are available in the short run, such a design can be completed successfully.[88,89] However, when differences are smaller or primary outcomes require long-term follow-up, adaptive randomization may not be feasible.

Although unbalanced randomization and play-the-winner strategies may reduce the number of subjects exposed to the inferior intervention, this advantage may be more than offset by the problem of justifying to those assigned to the nonpreferred arm why it is ethical for them to be recruited into the trial. Adaptive designs are also subject to methodological challenge, as changes in participants' prognostic profiles over the course of the trial (e.g., lesser severity of illness late in the trial) might lead to differences between groups and confound the interpretation of treatment effects.[90]

Yet another way to minimize suboptimal treatment for individual participants, as implemented by Kadane in a cardiac anesthesia trial,[91] involves Bayesian strategies for assigning study participants to treatment arms. Before the start of the trial, a group of experts made treatment recommendations for hypothetical patients with various prognostic profiles. These predictions were used to develop computer models that could provide treatment recommendations for individuals meeting the trial's eligibility criteria. Data that emerged over the course of the trial were used to update these models continually. If the experts' (computer-modeled) recommendations for a particular eligible patient unanimously favored one arm, the patient was assigned to that arm. In contrast, if there was any disagreement among the recommendations, clinical equipoise was said to exist and the patient underwent random allocation. This method has the virtue of individualization and might reduce assignment of patients to predictably inferior therapy, but is labor intensive and has not found widespread acceptance.

Two other proposals for reducing the tension between experimental validity and personal care merit consideration. First, Peto et al.[2] have advocated the use of "large simple trials," rather than the more typical and highly regimented "explanatory" designs.[92] Such trials are distinguished by their broad eligibility criteria, reduced data collection requirements, and limited specification of treatments in the study beyond the particular intervention under evaluation.[49] From the point of view of reconciling research and treatment imperatives, such trials have the virtue of minimizing the experimental constraints and practical burdens that protocols place upon patients and physicians. As a result, they have many scientific advantages, including facilitating very large sample sizes, decreasing complexity and cost, enhancing the generalizability (external validity) of the study findings, and reducing the gap between the efficacy as measured in controlled settings and effectiveness as seen in ordinary practice.[93–96] They also reduce the gap between personal and protocol care. Thus, for compelling ethical as well as scientific reasons, they merit serious consideration.

Finally, Veatch[76] and Silverman[97] have advocated "semi-randomized" or "comprehensive cohort" trials on both ethical and methodological grounds. In such studies, patients are offered the choice of Treatment A, Treatment B, or random assignment. Analytically, the primary comparison involves only the randomized subjects. However, subjects who choose direct assignment to Treatment A or Treatment B constitute useful observational cohorts. In particular, outcomes within these groups can shed light on whether the results of the primary comparison are generalizable to the population of persons who would not accept randomization (and who might differ in systematic ways from those willing to be randomized). This approach offers randomization as a genuine choice, reducing the need for physicians to choose

between fidelity to patients as unique individuals and allegiance to the experimental method. Although one might worry that few patients offered participation in such a trial would accept random assignment, such unwillingness might cast doubt on the ethical justification for randomization in the first place. Several comprehensive cohort trials have been successfully conducted.[98–100]

Empirical Data

Though the relationship of normative to descriptive ethics is an uneasy one, some questions about the ethics of RCTs lend themselves to empirical answers.

How often do RCTs comparing experimental with standard therapies find the new treatment to be better? The observation that trials favor the experimental treatment most of the time would suggest the absence of systematic indifference within the institution of clinical trials. Knowledge of the proportion of past trials favoring the experimental treatment would also inform estimates of prior probabilities associated with future trials.[101] Most such studies have not found strong advantages to experimental treatment. Reviewing surgery and anesthesia trials, Gilbert et al. found reasonable symmetry between studies favoring the experimental treatment and those favoring the standard.[60] Colditz et al. came to similar conclusions in trials of medical therapies.[102] Chlebowski and Lillington observed that 16% of meeting abstracts describing RCTs of adjuvant therapy for localized breast cancer and only 2% of abstracts describing RCTs for metastatic breast cancer favored experimental treatment.[103] Machin et al. noted that 28% of published RCTs for solid tumors from the British Medical Research Council favored the experimental treatment.[104] Djulbegovic et al. reported that 44% of published RCTs for multiple myeloma favored the standard treatment, whereas 56% favored the innovation.[105] They also found that industry-sponsored and placebo-controlled trials were more likely than other trials to favor the innovation, raising concerns about systematic departure from indifference. Joffe et al. observed that 29% of adult cancer trials sponsored by a publicly funded U.S. cooperative group favored the experimental treatment, whereas only 3% favored the standard treatment; on average, experimental treatment was associated with a 20% improvement in anticancer efficacy when compared with standard treatment.[106] Finally, Soares et al. found no evidence that trials sponsored by a radiation oncology cooperative group favored the experimental treatment.[107]

Do RCTs proceed despite compelling prior evidence that one treatment is better? Lau et al. used cumulative meta-analysis to evaluate the strength of evidence over time for or against 15 interventions for myocardial infarction.[108] For some interventions, trials continued years after benefits had been shown with high confidence. For example, 15 RCTs of intravenous streptokinase (SK) were reported and 32,095 subjects enrolled after 1977, by which time SK had been proven superior to control with Cumulative $P < 0.001$. Similar results have been seen in other settings.[109,110] Such continuation of trials long after differences have been convincingly shown is difficult to defend on scientific or ethical grounds.

Do physicians have preferences for treatment arms, and do they affect recruitment? Though surprisingly few data are available, treatment preferences appear both to be common among physicians and to reduce their willingness to enroll patients. For example, Taylor et al. surveyed surgeons participating in a slow-accruing trial comparing mastectomy with local excision for breast cancer.[111] About 20% believed that one or the other treatment was inappropriate for patients. Other work has shown that many physicians are uncomfortable with randomization, either because of treatment preferences or because it seems to violate the norms of the patient-doctor relationship.[112,113] Alderson found that few health-care professionals thought indifference was possible for breast cancer trials.[114] Cheng et al. described how prior beliefs led investigators to reject an RCT of a promising new therapy for melioidosis, a life-threatening infectious disease, despite considerable uncertainty about the new therapy's effectiveness.[115] Finally, Clark et al. applied the term "jumping-the-gun" to refer to physicians' tendencies to treat patients off-protocol with interventions that have not yet been proven in RCTs, a phenomenon that probably reflects early loss of indifference among individual physicians.[116]

Do patients have preferences for treatment arms, and do those preferences affect their enrollment decisions? Few data characterize preferences among patients considering or enrolled in RCTs. Jenkins and Fallowfield asked approximately 200 cancer patients considering participation in RCTs about their reasons for accepting or declining trial entry.[55] Three-quarters of those interviewed decided to participate in the RCT. Approximately 80% of those who accepted the trial, versus 14% who declined, agreed that "either treatment in the trial would be suitable," suggesting that treatment preferences explain at least some patients' decisions not to enter the trial. Jack et al. observed similar effects.[117] A review of the literature on trial accrual concluded that "patient preferences for one of the study treatments . . . appear to limit their willingness to take part in randomized trials."[118] Finally, in a recent trial of a molecularly targeted agent for chronic myeloid leukemia, 18% of those assigned to the standard arm—versus only 2% of those assigned to the experimental arm—either withdrew consent or crossed over to the alternative treatment before meeting the study endpoint, indicating both strong preferences and a willingness to act on them.[119]

Beyond Equipoise: A Systematic Overview of Ethical Issues in RCTs

Although notions of equipoise have dominated debates over the ethics of RCTs, these trials raise many other challenging questions. A comprehensive discussion is beyond the scope of this chapter. Here, we attempt to identify issues of particular salience to RCTs, locate them within a general framework for judging the ethics of clinical research,[7] and briefly review the relevant literature. Table 24.4 provides an overview.

Social or Scientific Value

In general, whether a research question is worth asking is independent of the study design, and therefore the requirement for social value has no special implications for RCTs. However, as discussed above, new trials sometimes begin long after any reasonable uncertainty about the preferred intervention is re-

Table 24.4
Randomized Trials and the Criteria for Ethical Research

Criterion	*Issues and Questions Relevant to Randomized TrialsTCH*
Social or scientific value	Has the study question previously been answered? • Confirmatory trials • Cumulative meta-analyses • Objective of answering unresolved questions versus changing clinical practice
Scientific validity	How much incremental validity does the RCT offer, compared with alternate designs? What problems compromise the validity of RCTs in practice? • Subversion of randomization • Underpowered trials • Publication bias • Concerns about generalizability
Fair selection of participants	(No special problems related to randomized designs)
Favorable risk-benefit ratio	Do the study treatments satisfy the indifference requirement? • Loss of personal care • Loss of expected utility for some subjects Is there a generic benefit (trial effect) from RCT participation? When should a study be stopped? What should the control treatment be when there is no standard of care?
Independent review	(No special problems related to randomized designs)
Informed consent	Is informed consent always necessary? • Randomized consent (Zelen) design • Minimal-risk RCTs • Emergency exception research
Respect for potential and enrolled participants	Is withholding of information from trial participants acceptable? • Study arm assignment (blinding) • Interim results

solved.[108–110] The question of when to conduct a confirmatory trial is controversial,[1,84,120] and requires further normative exploration. The history of neonatal extracorporeal membrane oxygenation (ECMO) provides an illustrative example (see Box 24.2). Finally, performing a trial in hopes of influencing slow-to-change practice patterns, despite the fact that the study question has previously been answered, is ethically problematic.[120]

Scientific Validity

The primary justification for randomization is its ability to minimize bias compared with alternative allocation strategies. Few deny that RCTs offer scientific benefits, but their exact magnitude is a matter of contention.[121] Early reports suggested that studies using historical or concurrent nonrandomized controls overestimated benefits from experimental therapies, compared with RCTs, primarily because controls in RCTs often had better outcomes than controls in other designs.[102,122,123] Recent meta-analyses comparing randomized with nonrandomized studies, however, offer a more complicated picture. Concato et al.[124] and Benson and Hartz[125] found that effects observed in well-conducted nonrandomized controlled trials were similar to those seen in RCTs. In contrast, Ioannidis et al. found that discrepancies between randomized and nonrandomized trials were common, even when the latter were restricted to prospective comparisons.[126] Thus, in our view, further empirical work is needed to quantify the magnitude of the scientific benefits from RCTs.

Even assuming substantial incremental validity, several practical problems threaten RCTs' claim to methodological priority. First, inadequate allocation concealment raises questions about the assumption of baseline comparability.[127,128] Furthermore,

Box 24.2
Trials of Neonatal ECMO

By the early 1980s, uncontrolled case series suggested that certain critically ill neonates who were expected to die with conventional treatment could survive if treated with extracorporeal membrane oxygenation (ECMO), a complex, expensive, and risky new therapy. A group of investigators began an RCT to compare outcomes among infants treated with ECMO or conventional treatment.[88] Because the investigators' prior expectations strongly favored ECMO (before initiating the trial, the investigators expected a 90% chance of survival with ECMO and 10% chance of survival with conventional treatment), they adopted several unusual design features to ''soften the ethical dilemma.''[88] First, they employed single-consent prerandomization, whereby only parents of those infants assigned to experimental treatment (ECMO) were asked for permission to enroll their child.[158] Second, they used adaptive randomization (i.e., allocation probabilities increasingly favored the treatment that had been more successful among prior subjects).[87] When the study ended, 1 child had been assigned to conventional treatment and died, whereas 11 children had been assigned to ECMO and survived. This difference was statistically significant.

In 1986, investigators at Harvard initiated a second RCT of ECMO versus conventional treatment.[159] They justified another trial because ''the disparity in group size [in the first RCT] provided little concurrent experience concerning the relative efficacy of the two therapies,'' and because they were concerned that rapidly decreasing mortality rates with conventional treatment made using historical controls problematic. This trial also used single-consent prerandomization. In addition, it employed a different form of adaptive randomization whereby all infants were randomized to either ECMO or conventional treatment until there were four deaths in one arm, after which all subsequent infants were directly assigned to the favored treatment. In this trial, 6 out of 10 infants treated with conventional treatment, versus 19 out of 20 infants treated with ECMO, survived ($p < 0.05$).

Though ECMO subsequently entered standard practice in the United States, it was not accepted in the United Kingdom at the time. Thus U.K. physicians, dissatisfied with the methods employed in the trials described above, initiated a conventional RCT in 1993.[90] By the fifth interim analysis three years later, mortality was 54/92 (59%) in the conventional arm and 30/93 (32%) in the ECMO arm ($p = 0.0005$). Upon the recommendation of the DMC, the trial was closed. The appropriateness of conducting this trial, giving the prior evidence favoring ECMO, has been hotly debated.[120]

participants in some blinded trials may make informed guesses about their treatment assignments, raising the possibility of unacknowledged postrandomization biases.[129,130] Second, many RCTs are underpowered, increasing the prevalence of false-negative results.[131] Third, evidence of publication bias (i.e., lower publication rates among negative than among positive RCTs) suggests that the literature systematically overstates the effectiveness of new treatments.[132–138] Fourth, participants in RCTs are often unrepresentative of the populations to which inferences are made, raising concerns that study results may not generalize to nontrial practice.[94,95,139–143] Fifth, despite RCTs' methodological rigor, bias may creep into authors' qualitative conclusions.[144]

Finally, Wikler argues that the standard *P* value cutoff of 0.05 for declaring statistical significance is "not a medical or statistical truth, but a clinician's convention."[57] It reflects a value-laden tradeoff between expected risks and benefits for present subjects and the degree of confidence desired before adopting new therapies. Also, as noted previously, because the *P* value fails to take into account the prior probability that the new treatment is superior to the standard, it can encourage misleading conclusions about the likelihood that an observed difference is a false positive.[14,16] Various strategies to deal with the practical and inferential problems of the *P* value, including relaxing the traditional 0.05 cutoff for rare diseases or low-risk/low-cost interventions and using Bayesian or mixed frequentist-Bayesian analytic techniques, have been proposed.[13,14,16,145–147]

Favorable Risk-Benefit Ratio

The Belmont Report enjoins us to consider risks and benefits to study participants, together with societal benefits from the knowledge gained, in evaluating the risk-benefit ratio of a particular study.[67] As Miller and Brody point out, the societal advantages of rigorous research design strengthen the ethical argument for RCTs, even when the indifference claim is weak.[66] On the other hand, RCTs open up the possibility that some participants may be disadvantaged by assignment to a predictably inferior therapy.[25] As we noted previously, the various conceptions of indifference in part represent efforts to resolve this conundrum. DMCs and early stopping rules are further efforts to walk the tightrope between advantages to society and costs to present patients.

It is difficult to estimate how much benefit, if any, subjects forgo by taking part in RCTs. Scant data indicate that experimental therapies in RCTs offer at best a small advantage over standard therapies.[60,103–106] However, some claim the existence of a benefit from trial participation itself,[25,148–150] though one of us has questioned the methodological basis for this conclusion.[151] In any case, the weight of evidence suggests that in most cases one sacrifices little or nothing in terms of disease outcome by agreeing to participate in an RCT.

Recently, controversy has erupted over whether RCTs with mortality or major morbidity endpoints must include standard-care control arms.[152–155] This debate, inspired by a trial involving patients with acute respiratory distress syndrome (ARDS), raises important questions of social value, scientific validity and risk-benefit ratio[156] (see Box 24.3).

In the ARDS trial, subjects were randomized to receive either large or small tidal volumes delivered by a mechanical ventilator, in which either option was judged at the start of the trial to be within the range of acceptable care. This design presented at least three questions at the interface of ethics and scientific methodology: (1) In the absence of a routine-care control arm (that is, a third arm of the trial in which tidal volumes would have been determined by the bedside clinicians), could the trial determine whether either treatment under study was preferable to current practice? (2) Were subjects randomized to either arm put at unnecessary risk compared with routine care? (3) Did the absence of a routine-care arm hinder the DMC's ability to evaluate whether participants were experiencing adverse outcomes using interim data?[152,157] Answering these questions is complex. Some have argued, for example, that a routine-care arm would not have been helpful in this trial, because routine care was not defined and was known to vary across a wide spectrum of practice. This lack of definition might have rendered any comparisons between the experimental arms and the routine-care control arm uninterpretable. At a minimum, the debate highlights the critical question

Box 24.3
The ARDSNet Controversy

In 1996, the Acute Respiratory Distress Syndrome Network (ARDSNet) initiated a multicenter randomized trial comparing mortality among critically ill patients treated with ''traditional'' high-volume mechanical ventilator breaths versus those treated with low-volume breaths.[156] At the start of the trial, practice varied considerably across intensive care units, with some preferring lower-volume and others higher-volume approaches. In addition, physicians generally adjusted their approach to mechanical ventilation based on the patient's clinical state. There was no consensus about the preferred ventilator strategy.

Against this background, trial participants were randomized to receive either high-volume or low-volume mechanical ventilation, with subsequent adjustments based on prespecified physiologic criteria. The high-volume strategy reflected approximately the 80th percentile of common practice, whereas the low-volume strategy reflected approximately the 3rd percentile.[153] About 860 subjects enrolled. In 1999, upon the recommendation of the Data Monitoring Committee (DMC), the trial closed early when convincing evidence for reduced mortality in the lower-volume arm emerged.

In July 2002, two critical-care physicians and two statisticians raised concerns about the trial, as well as about a second ARDSNet trial that was under way, with the Office for Human Research Protections (OHRP), which has regulatory jurisdiction over most U.S. human subjects research.[153] They argued that the absence of a routine-care control arm (either individualized ventilator management or volumes reflecting approximately the median in routine practice) potentially put subjects at increased risk. The additional risk could derive from the assignment of some participants to an inappropriate ''control'' arm, or from the inability of the DMC to monitor directly whether the participants in the two arms were experiencing poorer outcomes than they would have if they had received routine care. In response to this and other complaints, OHRP launched an investigation of the completed trial and requested that a second ARDSNet trial raising similar issues be suspended. Though ultimately it exonerated both trials and permitted the second trial to proceed, OHRP called for further debate about whether trials should be required on ethical grounds to include a routine-care control arm.[157]

of what role research ethics should play with regard to considerations of scientific design.[155]

Informed Consent

In general, informed consent to RCTs does not raise qualitatively different concerns from consent to other forms of intervention research. As with other designs, consent to RCTs is viewed by most as central to individuals' acceptance of the role of subject in addition to (or instead of) that of patient. However, several issues specific to RCTs have arisen.

Discomfort among physician-investigators with the mandate to obtain written informed consent has contributed to recruitment problems and even threatened the completion of some trials.[111] One response to this problem, advocated by Zelen, is to randomize eligible patients before requesting consent.[158] Investigators could then request consent only from those assigned to the experimental arm (single-consent design), or from those assigned to both arms (double-consent design). In either case, the trial would be analyzed on the basis of initial group assignment rather than treatment received (i.e., intent to treat). The single-consent approach, which withholds material information from some subjects, was deemed unethical by the U.S. National Institutes of Health when used in the Harvard Neonatal ECMO Trial.[89,159] The double-consent strategy is more palatable, though it too has been challenged on both ethical and methodological grounds. For example, Ellenberg[160] and Altman et al.[161] have argued that because of subject refusal and the need for intention-to-treat analyses, prerandomized trials may underestimate treatment effects and have reduced power when compared with conventional RCTs. Prerandomization is also inapplicable to blinded trials. Furthermore, it is possible that unbalanced presentations by investigators[162] (i.e., emphasizing benefits to those assigned to experimental therapy and uncertainty or risks to those assigned to standard therapy) or investigators' glossing over the difficult issue of randomization itself might lead subjects to consent who would have refused under the conventional design. On the basis of these arguments, Marquis has condemned prerandomization as "either unnecessary or unethical."[163]

Truog et al. have argued that informed consent to RCT participation may be ethically optional under limited circumstances, including (1) availability of all treatments outside the trial without the requirement for consent, (2) minimal incremental risk, (3) "genuine clinical equipoise," and (4) no basis for treatment preference among reasonable persons.[164] Middle-ground alternatives, such as opt-out consent designs,[165] are also available.

Trialists, ethicists, and regulators have recognized the impossibility of obtaining informed consent or proxy permission in some emergency trials, such as those for cardiac arrest[166] (see Chapter 27). In the United States, regulators have waived the requirement for informed consent to such trials if certain stipulations, including advance community consultation and notification, are met.[167] This emergency exception, although controversial, suggests that informed consent is not seen as ethically mandatory for all RCTs.

Empirical data on participants' or proxies' understanding of randomization are conflicting.[25] Several studies demonstrate problems with recognition of the method of treatment allocation or the underlying rationale for its use.[168–174] Other studies, however, paint a less pessimistic picture.[175–178]

Respect for Potential and Enrolled Participants

Emanuel et al. suggest that respect for subjects includes permitting withdrawal, protecting privacy, informing subjects of newly discovered risks or benefits, sharing results, and maintaining subject welfare.[7] For the most part, respect for subjects in RCTs raises no unique issues. One major difference, however, is that withholding information about treatment assignment and interim results is more common in RCTs than in other study designs.

Despite the fact that blinding challenges obligations of personal care as much as randomization (indeed, its methodological rationale is in part to preclude personal care),[179] it has received far less attention in the ethics literature. Clinicians who take part in blinded trials cannot easily make individualized dose adjustments, have difficulty interpreting adverse events, and may struggle with drug interactions. Although well-designed protocols will help investigators minimize risks to subjects as they navigate most situations, unanticipated circumstances can arise. Most commentators accept blinding if prospective subjects are aware of and agree to the fact that neither they nor the investigator will know their treatment assignment.[1,180] Nevertheless, this reliance on consent raises problems for pediatric and other research that relies on proxy permission. In such trials, blinding (a clearly nontherapeutic procedure) might be ethically justified if it was both scientifically necessary and involved at most a minor increment over minimal risk.[37,181]

Finally, respect for subjects would ordinarily include access to interim findings. The common practice of withholding interim results in RCTs further impairs personal care and increases the likelihood that subjects will receive a less effective treatment despite mounting evidence for its inferiority. At the same time, it may be practically necessary for trials to reach completion. As discussed above, withholding results is usually justified by reference to subjects' prior consent.[1,76,180] Some commentators, however, argue that such "consent" to ignorance is invalid, at least in certain circumstances, and that trial results should be freely available.[75,76] As with blinding, an alternate defense of the practice of withholding interim results might invoke methodological necessity and limited incremental risk.[37,181]

Study Design and Policy Implications

The appropriate methodological and policy response to the debates over RCTs depends largely on whether one agrees with Freedman and his followers that clinical equipoise succeeds in reconciling perfectly clinicians' obligations to help advance medical science and to care for individual patients. The main practical effect of adopting this position is to prohibit trials, especially involving placebo controls, in which equipoise does not obtain.[10–12] If, however, one believes as we do that RCTs (along with virtually all clinical research) may require accommodation between clinical and scientific commitments, the policy implications are more profound. At the extreme, viewing obligations to patients as absolute may require abandoning RCTs entirely.[23] Less radically,

one can seek to reduce inconsistencies between the clinical and scientific objectives of providing care within RCTs and to justify any compromises that remain. Several design and policy options merit consideration.

1. *Allocating treatments in ways that minimize losses to current patients:* Adaptive randomization and Bayesian allocation techniques might enhance expected utility for prospective subjects. Nevertheless, they do not entirely negate the charge that RCTs may require sacrificing the interests of some patients in pursuit of medical progress.[28,57]

2. *Expanding the range of choices available to patients:* When experimental treatments are available outside trials, patients could be offered the choice of randomization or direct assignment to standard or experimental therapy.[76] This would diminish concerns that the withholding of patients' (or their physicians') preferred treatment compels enrollment in RCTs. However, few data indicate whether participation in the primary analytic (i.e., randomized) groups would be sufficient to make this design feasible in practice.

3. *Conducting pragmatic trials:* In some circumstances, pragmatic trials, including large simple trials, may help reconcile the competing aims of RCTs without compromising scientific rigor.[2,49,93,182] In such trials, deviations from standard care are kept to the minimum necessary for experimental validity. In addition to the ethical advantages, proponents make scientific (enhanced generalizability) and logistical (lower cost, easier recruitment) arguments for such trials. Taken together, they form a compelling case for conducting a pragmatic trial when it can successfully answer the study question.

4. *Exploring Bayesian analytic techniques:* The implications of Bayesian statistical analysis for ethical conceptions of RCTs have received little attention. On the one hand, they might result in continuing trials beyond their stopping point under the frequentist paradigm, thus straining the indifference requirement past the point required by the $P = 0.05$ convention.[14,16] At the same time, by reminding us that both patients and physicians generally hold prior probabilities, Bayesian approaches could force greater emphasis on disclosure of preferences and on patient choice than is currently the norm.[43]

5. *Maximizing the return on investment from every RCT:* If the pursuit of scientific rigor through RCTs involves some concessions by present patients, then practical problems that compromise the quality of the information gained are especially troubling. Regarding publication bias, for example, one response envisions mandatory prospective registration of every RCT in a publicly accessible database.[183–184] Efforts to ensure that trials are adequately powered and to assess their generalizability to the populations of interest are also warranted.

6. *Weighing alternate designs:* Fried argued that proponents of RCTs wrongly characterize their advantages over other designs as "a gulf as sharp as that between the kosher and the non-kosher."[22] Nonrandomized concurrent controls, historical controls, or continuous quality improvement may occasionally offer feasible alternatives when RCTs prove ethically or practically untenable.[28,89,115,185] Shatz has written that "researchers ought to utilize alternative designs when they seem scientifically appropriate, and perhaps even when loss of scientific accuracy—which translates into possible losses for future patients—can be justified by reference to the interests of present patients."[24] At the same time, recent trials of high-dose chemotherapy for metastatic breast cancer[186] and of hormone replacement therapy for postmenopausal women[187] illustrate the dangers of relying on nonrandomized evidence. In our view, to avoid RCT orthodoxy investigators should consider alternative designs in each controversial case and provide specific justification for the decision to proceed with a randomized design.

Unresolved Ethical Issues and Data Requirements

Our review of the literature demonstrates four major areas that require additional data or greater conceptual clarity.

First, limited empirical evidence about the methodological or practical consequences of alternative designs exists. For example, how would comprehensive cohort designs affect trial enrollment and interpretation? How often do the restrictive eligibility criteria and tightly controlled conditions of many RCTs lead to answers that are internally valid but poorly generalizable to the population of interest?[189] How much bias is introduced by using concurrent but nonrandomized controls together with statistical adjustment techniques?[124,125] Answers to these questions are crucially important to informed policy decisions about clinical research.

Second, the views of prospective participants about the tradeoffs inherent in RCTs are poorly understood. For example, we know little about how individuals who enroll in trials view their status as both patient and subject, how often they have preferences for standard or experimental therapy, what reasons they hold for accepting randomization, or how they view the relationship between their own medical care and contributing to medical progress.

Third, the choices we make when defining the boundaries of uncertainty require explicit justification in full view of their consequences for patients and subjects.[82] Because they attempt to estimate treatment effects and their attendant uncertainties directly, Bayesian methods may prove especially fruitful here.[16]

Finally, despite the extensive debates over the past half-century, there is as yet no agreement on the fundamental justification for or appropriate use of randomized trials. Thus there is an overarching need for conversation among patients, methodologists, clinicians, and ethicists about the moral basis of RCTs. Existing writings, although rich and professionally diverse, do not always demonstrate the kind of interdisciplinarity or empirical grounding required to advance the debate. Because randomization largely highlights rather than fundamentally alters the dilemmas that are integral to most intervention studies, such conversation should transcend the narrow context of RCTs and aspire to articulate a solid ethical foundation for all clinical research.

References

1. Levine RJ. *Ethics and Regulation of Clinical Research,* 2nd ed. New Haven, Conn.: Yale University Press; 1986.
2. Peto R, Collins R, Gray R. Large-scale randomized evidence: Large, simple trials and overviews of trials. *Journal of Clinical Epidemiology* 1995;48:23–40.
3. Department of Health and Human Services, Office for Human Research Protections. *Protecting Human Research Subjects: Institutional Review Board Guidebook.* Rockville, Md.: OHRP; 1993. [Online] Available: http://www.hhs.gov/ohrp/irb/irb_guidebook.htm.

4. Ashcroft R. Equipoise, knowledge and ethics in clinical research and practice. *Bioethics* 1999;13:314–26.
5. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: Ethical and scientific issues. *Annals of Internal Medicine* 2000;133:455–63.
6. Harrington DP. The randomized clinical trial. *Journal of the American Statistical Association* 2000;95:312–5.
7. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000;283:2701–11.
8. Palmer CR. Ethics and statistical methodology in clinical trials. *Journal of Medical Ethics* 1993;19:219–22.
9. Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: Practical issues and specific cases. *Annals of Internal Medicine* 2000;133:464–70.
10. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *New England Journal of Medicine* 1994;331:394–8.
11. Freedman B, Weijer C, Glass KC. Placebo orthodoxy in clinical research. I: Empirical and methodological myths. *Journal of Law, Medicine, and Ethics* 1996;24:243–51.
12. Freedman B, Glass KC, Weijer C. Placebo orthodoxy in clinical research. II: Ethical, legal, and regulatory myths. *Journal of Law, Medicine, and Ethics* 1996;24:252–9.
13. Goodman SN. Toward evidence-based medical statistics. 1: The P value fallacy. *Annals of Internal Medicine* 1999;130:995–1004.
14. Lee SJ, Zelen M. Clinical trials and sample size considerations: Another perspective. *Statistical Science* 2000;15:95–110.
15. Spiegelhalter DJ, Freedman LS. Bayesian approaches to randomized trials. *Journal of the Royal Statistical Society A* 1994;157:357–416.
16. Goodman SN. Toward evidence-based medical statistics. 2: The Bayes factor. *Annals of Internal Medicine* 1999;130:1005–13.
17. Lewis RJ, Wears RL. An introduction to the Bayesian analysis of clinical trials. *Annals of Emergency Medicine* 1993;22:1328–36.
18. Walker AM, Barnwell JB. Clinical evaluation of chemotherapeutic drugs in tuberculosis. *Annals of the New York Academy of Sciences* 1949;52:742–9.
19. Fisher RA. Cigarettes, cancer and statistics. *Centennial Review* 1958;2:151–66.
20. Hill AB. Medical ethics and controlled trials. *British Medical Journal* 1963:1043–9.
21. Doll R. Controlled trials: The 1948 watershed. *British Medical Journal* 1998;317:1217–20.
22. Fried C. *Medical Experimentation: Personal Integrity and Social Policy*. New York, N.Y.: American Elsevier Publishing Co., Inc.; 1974.
23. Hellman S, Hellman DS. Of mice but not men: Problems of the randomized clinical trial. *New England Journal of Medicine* 1991;324:1585–9.
24. Shatz D. Randomized clinical trials and the problem of suboptimal care: An overview of the controversy. *Cancer Investigation* 1990;8:191–205.
25. Edwards SJ, Lilford RJ, Braunholtz DA, et al. Ethical issues in the design and conduct of randomised controlled trials: A review. *Health Technology Assessment* 1998;2(15):1–132.
26. Hellman S. The patient and the public good. *Nature Medicine* 1995;1:400–2.
27. Lilford RJ, Jackson J. Equipoise and the ethics of randomization. *Journal of the Royal Society of Medicine* 1995;88:552–9.
28. Royall RM. Ethics and statistics in randomized clinical trials. *Statistical Science* 1991;6:52–62.
29. Hellman D. Evidence, belief, and action: The failure of equipoise to resolve the ethical tension in the randomized clinical trial. *Journal of Law, Medicine, and Ethics* 2002;30:375–80.
30. Gifford F. Community-equipoise and the ethics of randomized clinical trials. *Bioethics* 1995;9:127–48.
31. Markman M. Ethical difficulties with randomized clinical trials involving cancer patients: Examples from the field of gynecologic oncology. *Journal of Clinical Ethics* 1992;3:193–5.
32. Menikoff J. The hidden alternative: Getting investigational treatments off-study. *Lancet* 2003;361:63–7.
33. Menikoff J. Full disclosure: Telling patients when not being a research subject is a good choice. *Perspectives in Biology and Medicine* 2005;48(Suppl.):S139–S149.
34. Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False hopes and best data: Consent to research and the therapeutic misconception. *Hastings Center Report* 1987;17(2):20–4.
35. Sordillo PP, Schaffner KF. The last patient in a drug trial. *Hastings Center Report* 1981;11(6):21–3.
36. Freedman B. Equipoise and the ethics of clinical research. *New England Journal of Medicine* 1987;317:141–5.
37. Weijer C. The ethical analysis of risk. *Journal of Law, Medicine, and Ethics* 2000;28:344–61.
38. Weijer C, Miller PB. When are research risks reasonable in relation to anticipated benefits? *Nature Medicine* 2004;10:570–3.
39. Gifford F. Freedman's "clinical equipoise" and "sliding-scale all-dimensions-considered equipoise." *Journal of Medicine and Philosophy* 2000;25:399–426.
40. Miller PB, Weijer C. Rehabilitating equipoise. *Kennedy Institute of Ethics Journal* 2003;13:93–118.
41. Angell M. Patients' preferences in randomized clinical trials. New England Journal of Medicine 1984;310:1385–7.
42. Marquis D. How to resolve an ethical dilemma concerning randomized clinical trials. *New England Journal of Medicine* 1999;341:691–3.
43. Lilford RJ. Ethics of clinical trials from a Bayesian and decision analytic perspective: Whose equipoise is it anyway? *British Medical Journal* 2003;326:980–1.
44. Ashcroft R. Giving medicine a fair trial: Trials should not second guess what patients want. *British Medical Journal* 2000;320:1686.
45. Veatch RM. Indifference of subjects: An alternative to equipoise in randomized clinical trials. *Social Philosophy and Policy* 2002;19:295–323.
46. Menikoff J. Equipoise: Beyond rehabilitation? *Kennedy Institute of Ethics Journal* 2003;13:347–51.
47. Karlawish JH, Lantos J. Community equipoise and the architecture of clinical research. *Cambridge Quarterly of Healthcare Ethics* 1997;6:385–96.
48. Sackett DL. Why randomized controlled trials fail but needn't: 1. Failure to gain "coal-face" commitment and to use the uncertainty principle. *Canadian Medical Association Journal* 2000;162:1311–4.
49. Peto R, Baigent C. Trials: The next 50 years. Large scale randomised evidence of moderate benefits. *British Medical Journal* 1998;317:1170–1.
50. Pocock SJ. When to stop a clinical trial. *British Medical Journal* 1992;305:235–40.
51. Enkin MW. Clinical equipoise and not the uncertainty principle is the moral underpinning of the randomised controlled trial: Against. *British Medical Journal* 2000;321:757–8.
52. Sackett DL. Equipoise, a term whose time (if it ever came) has surely gone. *Canadian Medical Association Journal* 2000;163:835–6.
53. Meier P. Terminating a trial—The ethical problem. *Clinical Pharmacology and Therapeutics* 1979;25:633–40.
54. Royall RM. Ignorance and altruism. *Journal of Clinical Ethics* 1992;3:229–30.
55. Jenkins V, Fallowfield L. Reasons for accepting or declining to participate in randomized clinical trials for cancer therapy. *British Journal of Cancer* 2000;82:1783–8.
56. Gifford F. The conflict between randomized clinical trials and the therapeutic obligation. *Journal of Medicine and Philosophy* 1986;11:347–66.

57. Wikler D. Ethical considerations in randomized clinical trials. *Seminars in Oncology* 1981;8:437–41.
58. Caplan AL. Is there a duty to serve as a subject in biomedical research? In: Caplan AL. *If I Were a Rich Man Could I Buy a Pancreas?* Bloomington, Ind.: Indiana University Press; 1992:85–99.
59. Almy TP. Meditation on a forest path. *New England Journal of Medicine* 1977;297:165–7.
60. Gilbert JP, McPeek B, Mosteller F. Statistics and ethics in surgery and anesthesia. *Science* 1977;198:684–9.
61. Mosteller F. Innovation and evaluation. *Science* 1981;211:881–6.
62. Marquis D. Leaving therapy to chance. *Hastings Center Report* 1983;13(4):40–7.
63. McDermott W. The changing mores of biomedical research. II. Challenge and discussion: Opening comments. *Annals of Internal Medicine* 1967;67(Supp1.7):39–42.
64. Eisenberg L. The social imperatives of medical research. *Science* 1977;198:1105–10.
65. Lasagna L. Some ethical problems in clinical investigation. In: Mendelsohn E, Swazey JP, Taviss I, eds. *Human Aspects of Biological Innovations.* Cambridge, Mass.: Harvard University Press; 1971:98–110.
66. Miller FG, Brody H. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *Hastings Center Report* 2003;33(3):19–28.
67. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* Washington, D.C.: Department of Health, Education and Welfare; DHEW Publication OS 78-0012 1978. [Online] April 18, 1979. Available: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm.
68. Miller FG. Research ethics and misguided moral intuition. *Journal of Law, Medicine, and Ethics* 2004;32:111–6.
69. Brody H, Miller FG. The clinician-investigator: Unavoidable but manageable tension. *Kennedy Institute of Ethics Journal* 2003;13:329–46.
70. Miller FG, Rosenstein DL. The therapeutic orientation to clinical trials. *New England Journal of Medicine* 2003;348:1383–6.
71. Grunberg SM, Cefalu WT. The integral role of clinical research in clinical care. *New England Journal of Medicine* 2003;348:1386–8.
72. Weijer C, Miller PB. Therapeutic obligation in clinical research. *Hastings Center Report* 2003;33(3):3.
73. Chalmers TC, Block JB, Lee S. Controlled studies in clinical cancer research. *New England Journal of Medicine* 1972;287:75–8.
74. Brody BA. *The Ethics of Biomedical Research: An International Perspective.* New York, N.Y.: Oxford University Press; 1998.
75. Lilford RJ, Braunholtz D, Edwards S, Stevens A. Monitoring clinical trials—Interim data should be publicly available. *British Medical Journal* 2001;323:441–2.
76. Veatch RM. *The Patient as Partner: A Theory of Human-Experimentation Ethics.* Bloomington, Ind.: Indiana University Press; 1987.
77. Baum M, Houghton J, Abrams K. Early stopping rules—Clinical perspectives and ethical considerations. *Statistics in Medicine* 1994;13:1459–69.
78. DeMets DL, Pocock SJ, Julian DG. The agonising negative trend in monitoring of clinical trials. *Lancet* 1999;354:1983–8.
79. Parmar MK, Griffiths GO, Spiegelhalter DJ, Souhami RL, Altman DG, van der Scheuren E. Monitoring of large randomised clinical trials: A new approach with Bayesian methods. *Lancet* 2001;358:375–81.
80. Bryant J, Wolmark N. Letrozole after tamoxifen for breast cancer—What is the price of success? *New England Journal of Medicine* 2003;349:1855–7.
81. National Breast Cancer Coalition. NBCC Raises Concerns About Halting of Letrozole Clinical Trial. [Online] 2003. Available: http://www.natlbcc.org/bin/index.asp?strid=627&btnid=1&depid=20.
82. Lantos JD, Frader J. Extracorporeal membrane oxygenation and the ethics of clinical research in pediatrics. *New England Journal of Medicine* 1990;323:409–13.
83. Food and Drug Administration. *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products.* Rockville, Md.: FDA; 1998. [Online] May, 1998. Available: http://www.fda.gov/cder/guidance/1397fnl.pdf.
84. Parmar MK, Ungerleider RS, Simon R. Assessing whether to perform a confirmatory randomized clinical trial. *Journal of the National Cancer Institute* 1996;88:1645–51.
85. Avins AL. Can unequal be more fair? Ethics, subject allocation, and randomised clinical trials. *Journal of Medical Ethics* 1998;24:401–8.
86. Palmer CR, Rosenberger WF. Ethics and practice: Alternative designs for phase III randomized clinical trials. *Controlled Clinical Trials* 1999;20:172–86.
87. Zelen M. Play-the-winner rule and the controlled clinical trial. *Journal of the American Statistical Association* 1969;64:131–46.
88. Bartlett RH, Roloff DW, Cornell RG, Andrews AF, Dillon PW, Zwischenberger JB. Extracorporeal circulation in neonatal respiratory failure: A prospective randomized study. *Pediatrics* 1985;76:479–87.
89. Truog RD. Randomized controlled trials: Lessons from ECMO. *Clinical Research* 1992;40:519–27.
90. UK Collaborative ECMO Trial Group. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet* 1996;348:75–82.
91. Kadane JB, ed. *Bayesian Methods and Ethics in a Clinical Trial Design.* New York, N.Y.: John Wiley and Sons, Inc.; 1996.
92. Sackett DL, Gent M. Controversy in counting and attributing events in clinical trials. *New England Journal of Medicine* 1979;301:1410–2.
93. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy. *JAMA* 2003;290:1624–32.
94. George SL. Reducing patient eligibility criteria in cancer clinical trials. *Journal of Clinical Oncology* 1996;14:1364–70.
95. Fuks A, Weijer C, Freedman B, Shapiro S, Skrutkowska M, Riaz A. A study in contrasts: Eligibility criteria in a twenty-year sample of NSABP and POG clinical trials. *Journal of Clinical Epidemiology* 1998;51:69–79.
96. Cochrane AL. *Effectiveness and Efficiency: Random Reflections on Health Services.* London, U.K.: Nuffield Provincial Hospitals Trust; 1972.
97. Silverman WA. Patient preferences and randomised trials. *Lancet* 1994;344:1023.
98. Link MP, Goorin AM, Miser AW, Green AA, Pratt CB, Belasco JB, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *New England Journal of Medicine* 1986;314:1600–6.
99. Schmoor C, Olschewski M, Schumacher M. Randomized and non-randomized patients in clinical trials: Experiences with comprehensive cohort studies. *Statistics in Medicine* 1996;15:263–71.
100. Henshaw RC, Naji SA, Russell IT, Templeton AA. Comparison of medical abortion with surgical vacuum aspiration: Women's preferences and acceptability of treatment. *British Medical Journal* 1993;307:714–7.
101. Chalmers I. What is the prior probability of a proposed new treatment being superior to established treatments? *British Medical Journal* 1997;314:74–5.
102. Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. I: Medical. *Statistics in Medicine* 1989;8:441–54.
103. Chlebowski RT, Lillington LM. A decade of breast cancer clinical investigation: Results as reported in the Program/Proceedings of the American Society of Clinical Oncology. *Journal of Clinical Oncology* 1994;12:1789–95.

104. Machin D, Stenning SP, Parmar MK, et al. Thirty years of Medical Research Council randomized trials in solid tumours. *Clinical Oncology* 1997;9:100–14.
105. Djulbegovic B, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, et al. The uncertainty principle and industry-sponsored research. *Lancet* 2000;356:635–8.
106. Joffe S, Harrington DP, George SL, Emanuel EJ, Budzinski LA, Weeks JC. Satisfaction of the uncertainty principle in cancer clinical trials: Retrospective cohort analysis. *British Medical Journal* 2004; 328:1463–7.
107. Soares HP, Kumar A, Daniels S, et al. Evaluation of new treatments in radiation oncology: Are they better than standard treatments? *JAMA* 2005;293:970–8.
108. Lau J, Antman EM, Jimenez-Silva J, et al. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *New England Journal of Medicine* 1992;327:248–54.
109. Clark O, Adams JR, Bennett CL, Djulbegovic B. Erythropoietin, uncertainty principle and cancer related anaemia. *BMC Cancer* 2002;2:23.
110. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts: Treatments for myocardial infarction. *JAMA* 1992;268:240–8.
111. Taylor KM, Margolese RG, Soskolne CL. Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer. *New England Journal of Medicine* 1984;310:1363–7.
112. Taylor KM, Feldstein ML, Skeel RT, Pandya KJ, Ng P, Carbone PP. Fundamental dilemmas of the randomized clinical trial process: Results of a survey of the 1,737 Eastern Cooperative Oncology Group investigators. *Journal of Clinical Oncology* 1994;12:1796–805.
113. Taylor KM. Physician participation in a randomized clinical trial for ocular melanoma. *Annals of Ophthalmology* 1992;24:337–44.
114. Alderson P. Equipoise as a means of managing uncertainty: Personal, communal and proxy. *Journal of Medical Ethics* 1996;22:135–9.
115. Cheng AC, Lowe M, Stephens DP, Currie BJ. Ethical problems of evaluating a new treatment for melioidosis. *British Medical Journal* 2003;327:1280–2.
116. Clark WF, Garg AX, Blake PG, Rock GA, Heidenheim AP, Sackett DL. Effect of awareness of a randomized controlled trial on use of experimental therapy. *JAMA* 2003;290:1351–5.
117. Jack WJ, Chetty U, Rodger A. Recruitment to a prospective breast conservation trial: Why are so few patients randomised? *British Medical Journal* 1990;301:83–5.
118. Gotay CC. Accrual to cancer clinical trials: Directions from the research literature. *Social Science and Medicine* 1991;33:569–77.
119. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *New England Journal of Medicine* 2003;348:994–1004.
120. Lantos JD. Was the UK collaborative ECMO trial ethical? *Paediatric and Perinatal Epidemiology* 1997;11:264–8.
121. Gehan EA, Freireich EJ. Non-randomized controls in cancer clinical trials. *New England Journal of Medicine* 1974;290:198–203.
122. Sacks H, Chalmers TC, Smith H, Jr. Randomized versus historical controls for clinical trials. *American Journal of Medicine* 1982;72: 233–40.
123. Miller JN, Colditz GA, Mosteller F. How study design affects outcomes in comparisons of therapy. II: Surgical. *Statistics in Medicine* 1989;8:455–66.
124. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *New England Journal of Medicine* 2000;342:1887–92.
125. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *New England Journal of Medicine* 2000;342:1878–86.
126. Ioannidis JP, Haidich AB, Pappa M, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. *JAMA* 2001;286:821–30.
127. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408–12.
128. Schulz KF. Subverting randomization in controlled trials. *JAMA* 1995;274:1456–8.
129. Byington RP, Curb JD, Mattson ME. Assessment of double-blindness at the conclusion of the beta-Blocker Heart Attack Trial. *JAMA* 1985;253:1733–6.
130. Howard J, Whittemore AS, Hoover JJ, Panos M. How blind was the patient blind in AMIS? *Clinical Pharmacology and Therapeutic* 1982;32:543–53.
131. Freiman JA, Chalmers TC, Smith H, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial: Survey of 71 "negative" trials. *New England Journal of Medicine* 1978;299:690–4.
132. Sterling TD. Publication decisions and their possible effects on inferences drawn from tests of significance—Or vice versa. *Journal of the American Statistical Association* 1959;54:30–4.
133. Rosenthal R. The "file drawer problem" and tolerance for null results. *Psychological Bulletin* 1979;86:638–41.
134. Dickersin K, Chan S, Chalmers TC, Sacks HS, Smith H. Publication bias and clinical trials. *Controlled Clinical Trials* 1987;8:343–53.
135. Dickersin K, Min YI. Publication bias: The problem that won't go away. *Annals of the New York Academy of Sciences* 1993;703:135–46.
136. Stern JM, Simes RJ. Publication bias: Evidence of delayed publication in a cohort study of clinical research projects. *British Medical Journal* 1997;315:640–5.
137. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. *JAMA* 1998;279:281–6.
138. Krzyzanowska MK, Pintilie M, Tannock IF. Factors associated with failure to publish large randomized trials presented at an oncology meeting. *JAMA* 2003;290:495–501.
139. Antman K, Amato D, Wood W, Carson J, Suit H, Proppe K, et al. Selection bias in clinical trials. *Journal of Clinical Oncology* 1985;3:1142–7.
140. Winger MJ, Macdonald DR, Schold SC, Jr., Cairncross JG. Selection bias in clinical trials of anaplastic glioma. *Annals of Neurology* 1989;26:531–4.
141. Cottin V, Arpin D, Lasset C, Cordier JF, Brune J, Chauvin F, et al. Small-cell lung cancer: Patients included in clinical trials are not representative of the patient population as a whole. *Annals of Oncology* 1999;10:809–15.
142. Bertelsen K. Protocol allocation and exclusion in two Danish randomised trials in ovarian cancer. *British Journal of Cancer* 1991;64:1172–6.
143. Ward LC, Fielding JW, Dunn JA, Kelly KA, for the British Stomach Cancer Group. The selection of cases for randomised trials: A registry survey of concurrent trial and non-trial patients. *British Journal of Cancer* 1992;66:943–50.
144. Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: A reflection of treatment effect or adverse events? *JAMA* 2003;290:921–8.
145. Tan SB, Dear KB, Bruzzi P, Machin D. Strategy for randomised clinical trials in rare cancers. *British Medical Journal* 2003;327:47–9.
146. Lagakos SW. Clinical trials and rare diseases. *New England Journal of Medicine* 2003;348:2455–6.
147. Slutsky AS. Prone positioning of patients with acute respiratory failure: The editorialist replies. *New England Journal of Medicine* 2002;346:297.
148. Lantos JD. The "inclusion benefit" in clinical trials. *Journal of Pediatrics* 1999;134:130–1.

149. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect." *Journal of Clinical Epidemiology* 2001;54:217–24.
150. Stiller CA. Centralised treatment, entry to trials and survival. *British Journal of Cancer* 1994;70:352–62.
151. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: Conceptual framework and structured review. *Lancet* 2004;363:263–70.
152. Miller FG, Silverman HJ. The ethical relevance of the standard of care in the design of clinical trials. *American Journal of Respiratory and Critical Care Medicine* 2004;169:562–4.
153. Steinbrook R. How best to ventilate? Trial design and patient safety in studies of the acute respiratory distress syndrome. *New England Journal of Medicine* 2003;348:1393–401.
154. Steinbrook R. Trial design and patient safety—The debate continues. *New England Journal of Medicine* 2003;349:629–30.
155. Drazen JM. Controlling research trials. *New England Journal of Medicine* 2003;348:1377–80.
156. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New England Journal of Medicine* 2000;342:1301–8.
157. Office for Human Research Protections. Letter to Lee E. Limbird, Associate Vice Chancellor for Research, Vanderbilt University, July 25, 2003. [Online] Available: http://www.hhs.gov/ohrp/detrm_letrs/YR03/ju103af.pdf.
158. Zelen M. A new design for randomized clinical trials. *New England Journal of Medicine* 1979;300:1242–5.
159. O'Rourke PP, Crone RK, Vacanti JP, et al. Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: A prospective randomized study. *Pediatrics* 1989;84:957–63.
160. Ellenberg SS. Randomization designs in comparative clinical trials. *New England Journal of Medicine* 1984;310:1404–8.
161. Altman DG, Whitehead J, Parmar MK, Stenning SP, Fayers PM, Machin D. Randomised consent designs in cancer clinical trials. *European Journal of Cancer* 1995;31A:1934–44.
162. Snowdon C, Elbourne D, Garcia J. Zelen randomization: Attitudes of parents participating in a neonatal clinical trial. *Controlled Clinical Trials* 1999;20:149–71.
163. Marquis D. An argument that all prerandomized clinical trials are unethical. *Journal of Medicine and Philosophy* 1986;11:367–83.
164. Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized, controlled trials? *New England Journal of Medicine* 1999;340:804–7.
165. Rogers CG, Tyson JE, Kennedy KA, Broyles RS, Hickman JF. Conventional consent with opting in versus simplified consent with opting out: An exploratory trial for studies that do not increase patient risk. *Journal of Pediatrics* 1998;132:606–11.
166. Biros MH, Lewis RJ, Olson CM, Runge JW, Cummins RO, Fost N. Informed consent in emergency research: Consensus Statement from the Coalition Conference of Acute Resuscitation and Critical Care Researchers. *JAMA* 1995;273:1283–7.
167. Department of Health and Human Services. Waiver of Informed Consent Requirements in Certain Emergency Research; Waiver. *Federal Register* 1996;61(192):51531–3. [Online] Available: http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc97–01.htm.
168. Kodish E, Eder M, Noll RB, Ruccione K, Lange B, Angiolillo A, et al. Communication of randomization in childhood leukemia trials. *JAMA* 2004;291:470–5.
169. van Stuijvenberg M, Suur MH, de Vos S, et al. Informed consent, parental awareness, and reasons for participating in a randomised controlled study. *Archives of Disease in Childhood* 1998;79:120–5.
170. Snowdon C, Garcia J, Elbourne D. Making sense of randomization: Responses of parents of critically ill babies to random allocation of treatment in a clinical trial. *Social Science and Medicine* 1997;45:1337–55.
171. Benson PR, Roth LH, Appelbaum PS, Lidz CW, Winslade WJ. Information disclosure, subject understanding, and informed consent in psychiatric research. *Law and Human Behavior* 1988;12:455–75.
172. Aaronson NK, Visser-Pol E, Leenhouts GH, et al. Telephone-based nursing intervention improves the effectiveness of the informed consent process in cancer clinical trials. *Journal of Clinical Oncology* 1996;14:984–96.
173. Simes RJ, Tattersall MH, Coates AS, Raghavan D, Solomon HJ, Smartt H. Randomised comparison of procedures for obtaining informed consent in clinical trials of treatment for cancer. *British Medical Journal* 1986;293:1065–8.
174. Davis SW, Nealon EO, Stone JC. Evaluation of the National Cancer Institute's clinical trials booklet. *Journal of the National Cancer Institute Monographs* 1993;14:139–45.
175. Howard JM, DeMets D. How informed is informed consent? The BHAT experience. *Controlled Clinical Trials* 1981;2:287–303.
176. Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent in cancer clinical trials: A cross-sectional survey. *Lancet* 2001;358:1772–7.
177. DCCT Research Group. Implementation of a multicomponent process to obtain informed consent in the Diabetes Control and Complications Trial. *Controlled Clinical Trials* 1989;10:83–96.
178. Coyne CA, Xu R, Raich P, et al. Randomized, controlled trial of an easy-to-read informed consent statement for clinical trial participation: A study of the Eastern Cooperative Oncology Group. *Journal of Clinical Oncology* 2003;21:836–42.
179. Vickers AJ, de Craen AJ. Why use placebos in clinical trials? A narrative review of the methodological literature. *Journal of Clinical Epidemiology* 2000;53:157–61.
180. Lantos J. Ethics, randomization, and technology assessment. *Cancer* 1994;74:2653–6.
181. Department of Health and Human Services, National Institutes of Health, and Office for Human Research Protections. The Common Rule, Title 45 (Public Welfare), Code of Federal Regulations, Part 46 (Protection of Human Subjects); Subpart D—Additional Protections for Children Involved as Subjects in Research. [Online] June 23, 2005. Available: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd.
182. Crouch RA. Eligibility, extrapolation and equipoise: Unlearned lessons in the ethical analysis of clinical research. *IRB: Ethics and Human Research* 2001;23(4):6–9.
183. Simes RJ. Publication bias: The case for an international registry of clinical trials. *Journal of Clinical Oncology* 1986;4:1529–41.
184. Dickersin K, Rennie D. Registering clinical trials. *JAMA* 2003;290:516–23.
185. Berwick DM. Harvesting knowledge from improvement. *JAMA* 1996;275:877–8.
186. Stadtmauer EA, et al., for the Philadelphia Bone Marrow Transplant Group. Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. *New England Journal of Medicine* 2000;342:1069–76.
187. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–3.
188. Weijer C, Shapiro SH, Glass KC. Clinical equipoise and not the uncertainty principle is the moral underpinning of the randomised controlled trial—for and against—education and debate. *British Medical Journal* 2000;321:756–8.
189. Vist GE, Hagen KB, Devereaux PJ, Bryant D, Kristoffersen DT, Oxman AD. Systematic review to determine whether participation in a trial influences outcome. *British Medical Journal* 2005;330:1175.