Bayesian Methods and Ethics in a Clinical Trial Design

Edited by
Joseph B. Kadane

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Bayesian Methods and Ethics in a Clinical Trial Design

Edited by

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Preface

The ideas in this book, the use of Bayesian methods to give patients a better break in clinical trials, have taken over a decade to bring to fruition. They have, in general, their technological roots in the development of Bayesian ideas, and in particular in progress in practical elicitation of prior opinions.

These ideas have been developed by a talented interdisciplinary group involving philosophy (Schaffner, Seidenfeld), law (Kairys), medicine (Heitmiller, Blanck), statistics (Kadane, Sedransk, Emrich), and statistical computing (Galway). This group was helped, critiqued, and commented upon by other participants, including Coulehan, Katz, Popp, and Moore. All have their say in the chapters that follow.

That each of these people has been trained in a particular way does lead to certain intellectual leanings on their part, but it does not determine their perspectives by any means. There was a lot of debate in our meetings, and we came to appreciate each other's viewpoints more as a result. We also came to see that we are all potential consumers of clinical research, and we are all potential patients in clinical trials as well. We are particularly reminded of the human stakes in our research by the untimely death of Larry Emrich, coauthor of Chapter 18 of this book.

My hope in editing this book is to provide some of the flavor of the debate. To do so, I have encouraged each author to tell a personal story in a personal way. The consequence is that the book is somewhat uneven from chapter to chapter. I hope that the burden on the reader imposed by this policy is compensated for by the genuineness of the resulting expression. The discussion did not always lead to agreement; sometimes we found the opinions of others wrong and/or offensive. In order to expose the variety of opinions offered, there are three chapters of commentary (7, 15, and 16), and one of rebuttal (17).

The book is organized as follows: Chapter 1 gives an overview of the project and touches on the main ideas. Most readers will be well served by reading it first. The next three chapters, constituting Part I, deal with important issues for the class of designs of clinical trials proposed here: Chapter 2, by Schaffner, reviews current ethical theory and how it relates to our design; Chapter 3, by

Sedransk, examines the key concept of the admissibility of a treatment assignment to a particular patient and offers advantages and disadvantages for each of the several choices. Finally, Chapter 4, written by Kadane and Seidenfeld, shows how the data from a trial designed as we suggest, can be analyzed to yield uncontaminated information about the effect of treatment on outcome. I think a first reader would want to at least skim these chapters.

The heart of the book is Part II, the test case of the verapamil/nitroprusside trial as agents for treatment of hypertension immediately after open-heart surgery. This material, in Chapters 5 through 13, discusses the process and results of the trial, as experienced by the investigators. Probably this will be the most heavily studied aspect of the book, since it is more specific than the generalities that precede and follow it.

Part III takes up other issues that we explored in this context. In Chapter 14 Kairys explores American law and how it relates to our design for a clinical trial. This chapter attracted comments from Popp and Moore, and from Katz, to which Kairys replies in Chapter 17. Each of the chapters in the legal section is dated to reflect when it was first written. Each of the authors had a recent opportunity to revise and declined to do so. Finally, Chapter 18 reports work by Sedransk and Emrich about when a rational patient would agree to participate in a clinical trial. The book concludes with an Epilogue in Chapter 19.

The work reported here is the subject of research funded by the Ethics and Values in Science and Technology Program of the National Science Foundation and by the National Endowment for the Humanities, through Carnegie Mellon University. Those supported by the grant included Lionel Galway, Joseph B. Kadane, David Kairys, Ken Schaffner, Nell Sedransk, and Teddy Seidenfeld, advised by Thomas J. J. Blanck, Jack Coulehan, Preston Covey, Jerome J. DeCosse, Arvin S. Glicksman, Eugenie Heitmiller, Rachelle Hollander, Kathryn D. Katz, Alan Meisel, A. John Popp, and John C. Ruckdeschel. Others whose comments were helpful include John Bailar III, Robyn Dawes, Clark Glymour, and Juana Sanchez. Chapters 1 and 12 appeared in earlier forms in the *Journal of Medicine and Philosophy*, 11 (1986), 325–404, and in the *Journal of Statistical Planning and Inference*, 40 (1994), 221–232, respectively.

J. B. KADANE

Pittsburgh, PA
September 1995

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PART I

Major Issues

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CHAPTER 1

Introduction

Joseph B. Kadane

The circumstances surrounding the administration of experimental drugs and treatments to human beings trouble the conscience of the medical and scientific community. Not that I think what is done is bad. On the whole the system works surprisingly well. There are a few atrocity cases, however. I remember especially the Tuskegee syphilis experiment, in which black men with syphilis remained untreated for years so that the experimenters could observe the natural course of the disease (Brandt 1978). But on the whole it is my belief that standard experimental practice takes reasonable care of patients in clinical trials. I think that experimentation bothers the conscience because it is not clear that the patient is receiving the best possible care in the experimental situation (see Lellouch and Schwartz 1971; Clayton 1982). This is a quest without a definite end: To be sure it is a challenge to our collective applied cleverness to see if we can somehow devise alternatives that are both arguably better for patients and scientifically responsible.

1.1 DO PATIENTS GET A FAIR SHAKE IN CURRENT CLINICAL TRIALS?

Most clinical trials use some form of randomization to assign patients to treatments. Patients may be told that the treatment they will be given is decided by the flip of a coin. Often this is not literally true, for neither the patient nor the attending physician knows which treatment will be assigned. The patient is asked to sign an informed-consent statement agreeing to be in the experiment, and agreeing to treatment assigned in a random manner. Informed consent is like a legal contract between the patient and the physician. Usually the contract states the patient's diagnosis, the treatments under study, and the possible adverse side effects of the treatments. On this basis the patient signs the form, accepting the randomly assigned treatment.

The informed-consent procedure affirms the rights of the patients to determine the uses of their bodies. But if informed consent is to be regarded as a valid contract, the patient and experimenter must be reasonably equal in

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bargaining power and have their wits about them. On this point the evidence is negative. In several studies the experimenter was in the waiting room to interview the patient leaving the physician's office after the informed-consent interview. The patients had poor recall of what they had signed and what the treatments and side effects were. Many patients had interpreted the process of informed consent as a form they had to sign in order to get treatment. (See Meisel and Roth 1983 for a review).

To say this is not to criticize the physicians or the patients. The patients are, after all, sick, and depending on the nature and severity of their illness, their cognitive functioning may be impaired. They may, earlier in the informed-consent interview or in the recent past, have been given bad news about their health or prognosis. Who among us might not be upset and functioning poorly when given such news? The physician and the patient are not anywhere near equal in bargaining power in this situation.

Despite the evidence showing that informed consent is rarely "informed" and may or may not be consent, I would not recommend abolishing the ceremony. Rather, my interpretation of these results is that they impose a greater burden on the medical-scientific community to ensure that the contract offered the patient in informed consent is as advantageous as possible for the patient. We must look out for the patient's interests, since the patient may be unable to do so. We cannot use the excuse that the patient has agreed, via informed consent, to a disadvantageous procedure. To do so has the ring of foisting disadvantageous treaties on Indian chiefs in a language they did not know.

So I am led to consider the fairness of the substance of what the patient is asked to sign in informed consent. Here the picture is somewhat gloomier. Let us accept that clinical trials only occur when the medical community is not agreed upon the best treatment for the condition under study. In such a circumstance the patient can be told truthfully that the best treatment among those compared in the trial is not currently known. But this does not justify random assignment. A knowledgeable patient might say, "Doctor, you know about me and about my disease. You must have a hunch about which treatment would be better for me. Please give me the treatment, and forget about flipping coins." If the attending physician is not so knowledgeable, we can suppose that a consulting expert could be found to make such a judgment. Even if such an expert were truly neutral at the start of a study, after the first few patients are studied and their outcomes are at least partially known, there would be a reasonable basis for a hunch that could be useful to the patient, though without the established validity we usually associate with scientific knowledge (see Chalmers 1967).

One road out of this conundrum is to keep the attending physicians ignorant of the results of the trial to date. This is useful in that it may help reduce their tendency, even unconsciously, to change the pool of patients in the trial or to misinterpret "recovery." But as a way to deal with the legitimate patient objective of getting competent and appropriate care, it seems to me to be very shaky. If anything, there might be a duty to inform the attending

physicians of the data to date so that their advice to, and treatment of, patients might be better informed. To prevent the person who is supposed to be using his or her expert judgment to help the patient from having the very information that might help the patient seems to me to be unethical. After all if that person had that information and conveyed it to the patient, the patient might make a decision the designers of the trial do not want the patient to make.

Sometimes a physician believes that a drug or treatment available only through a specific clinical trial would be advantageous to the patient. This argument presupposes the current U.S. law that requires FDA approval before a new drug can be made available commercially. It also assumes that the patient is unable or unwilling to go to another country where the treatment is available without being in a trial. Such availability of the treatment would mean that the patient could be certain of getting the treatment, without undergoing randomization. This is then a weak sense of advantageousness to patients, and it applies to only a few trials.

There is another line of argument that supports the current system from a very different premise. This line is utilitarian, and admits that the deal currently offered patients is suboptimal in a narrow accounting of the patient's interests. Quite frankly, the patient is being asked to sacrifice some prospect of recovery for the sake of scientific progress. Of course this is hubris, the kind of assertion that has led in our century to much good but also much mischief. I would feel more comfortable with it if I thought that informed consent worked better than it apparently does. While an appeal to this argument may in the end be necessary to support doing clinical trials on human beings at all, surely the circumstance that the patients, as a practical matter, are not in a good position to defend themselves from overly great and unfair claims that they should "help science" must admonish us to design trials to reduce the burden on patients to a minimum. Whether patients get a fair shake in current clinical trials, then, depends critically on our ability to propose a system that would be better for them and still permit the scientific analysis of the resulting data.

1.2 WHY ALLOWING PATIENTS TO CHOOSE THEIR OWN TREATMENTS IS NOT A SOLUTION

Clinical trials would be a fruitless exercise if the data could not be used scientifically. There is, in medicine, a long history of false conclusions reached through observational studies or from clinical trials lacking proper control. This has led the medical/scientific community to be methodologically cautious, and properly so.

To take a position opposite to current practice, suppose that the patient and the physician jointly decide on a treatment. The trial may then follow the course of the patient. This would remove nearly entirely the burden imposed by current trials on patients of being assigned a possibly disadvantageous treatment. However, how could interpreters of the data separate effects due to the treatments themselves from effects due to the kinds of people who choose

the treatments? To take a recent example, a study was done on women with breast cancer to determine whether segmental mastectomy, which removes only sufficient tissue to ensure that what remains is free of tumor, is as efficacious as the more traditional total mastectomy, which removes the entire breast and some chest muscles (Fisher et al. 1985). Women may value differently the benefits of saving the breast against the possible increased risk of recurrence of the cancer (and early death). How they do so may have something to do with their personality, which, for all we know now about cancer, may have something to do with their outcome. Consequently, had they been allowed to choose their own treatments, it would have been very difficult to interpret the results. A summary of the data might be "Among those who chose segmental mastectomy, the five-year survival rate was x, while among those who chose total mastectomy, the five-year survival rate was y." If $x > y$, the advice to patients is to be like those who chose segmental mastectomy. This is unhelpful both scientifically and therapeutically. I do not mean that such data must be valueless—as a statistician I occasionally work with data sets with as much ambiguity. But I do mean that, had it been required that patients be allowed to choose their treatments, it might well have been decided that such a study would not be a cost-effective way to make progress on cancer, and consequently the study might well not have been done. And this would have been a real loss to the thousands of women who develop breast cancer every year. We would not be doing a service if, in the name of protecting patients, we protected them from the possibility of medical progress using clinical trials. (For a contrary view outside of the context of experimentation, see Schultz 1985).

What I seek, then, is a middle position, one that offers patients a better deal in the design of a trial but that still offers data interpretable as bearing on the effect of the treatment on the disease. This will be a compromise of some sort. It is in the nature of compromises that they are uneasy positions, liable to attack from both sides.

1.3 DISAGREEMENT AMONG EXPERTS

Disagreement among medical experts about the advisable treatment for the condition seems inherent to the decision to conduct a clinical trial. Clinical trials are expensive, and, according to this model, will be conducted only when serious disagreement exists. Many medical procedures are supported by custom, and do not have a rigorous scientific basis, so orthodox treatment is not necessarily good medicine. The radical mastectomy operation for breast cancer, mentioned above, was the standard treatment since the turn of the century. A trial to compare it to the alternative lumpectomy was not begun until the mid-1970s, however, when sufficient expert opinion supported the alternative to create serious disagreement.

Sometimes there are trials where nearly the entire medical community is quite convinced of the outcome before the trial starts. This was the case in the

test of a derivative of apricot pits (Laetrile) as a treatment for terminal cancer. Although outlawed as a treatment in the United States, many very sick and desperate patients were going to Mexico for treatment using it, in the hope that it might be effective. Finally, sufficient political pressure was brought to bear through Congress on NIH that a clinical trial was authorized. (The treatment proved ineffective.)

What happened here, in my view, is that the definition of who is a medical expert was expanded to include physicians who believed in this unorthodox treatment. The lesson I learn from this episode is that the decisions as to who is an expert and what clinical trials will be conducted have a political component. Often expenditure of public money is involved. Always the credibility and trust put in the medical/scientific community by the public is at stake. While the politics involved rarely includes Congress, it usually does have to do with the pecking order among physicians and scientists (and also between physicians and scientists), which is political in the larger sense. I do not regard this as pejorative; I think of peer review as a political mechanism to reach political decisions about the allocation of resources. "Political" need not mean partisan in the sense of political parties. Modern scientific politics often involves fascinating mixtures of expertise and general judgment in matters such as environmental and space policy, energy, and the construction of large laboratories to study fundamental particles, as well as medicine. Whom to trust to do what is a matter of continuing discussion; I will return to this question later, after explaining the proposal discussed in this book, to show that the particular way information is treated here ameliorates this problem to some extent.

Disagreement in the medical community often colors what a physician might say to a patient about the relative merits of the treatments in a clinical trial. To say that the best treatment is not known is obvious. This usually does not imply that the physician has no opinion about which of the treatments might be better for the patient. I would argue that what a patient seeks from his or her physician is informed opinion. Medical certainty and agreement, although pleasant when available, are the exception. (This is not to deny the possible therapeutic benefit of a patient's naive belief in the infallibility of the physician.)

1.4 A PARTIAL REDEFINITION OF THE RESPONSIBILITIES OF THE DESIGNERS OF A CLINICAL TRIAL TO THE PATIENT

In the context of clinical trials medical experts will likely disagree about the desirability of the treatments. A responsible clinical trial cannot offer patients a choice of treatments. What might then be said about the responsibilities of the designers of a clinical trial to the patient?

For the long-term survival of clinical trials as well as for the shorter-term effect of feeling better about what one is doing, it seems to me that a clinical trial should offer the patient whatever benefits the patient might reasonably be

able to obtain outside the trial, as long as it can do so and still fulfill its scientific mission. What might this consist of in the context of lack of knowledge in the medical community and conflict over the best courses of treatment? Suppose that there is a group of experts on the disease, identified in the scientific-political way described above. A vigorous patient with adequate financial resources and good medical connections might get to see one of these experts and take the advice of that expert about what treatment to take. Thus I think that a clinical trial should try to replicate this, as best it can, for the patients in the trial.

A second thing I think a clinical trial ought to do is to offer information or use information developed during the course of the trial for the benefit of the patient to the extent that it can do so without jeopardizing the scientific merit of the study. The proviso is there because totally unblinded patients might implicitly be choosing their treatment in the guise of choosing whether to be in the trial. Thus, for example, in a randomized trial, telling the patient what treatment would be assigned if the patient were in the trial, might have this effect. There can be legitimate differences of opinion about what information might "jeopardize the scientific merit of the study," a matter to which this chapter returns later.

1.5 THE BASICS OF SUBJECTIVE STATISTICAL INFERENCE

There are several forms of classical statistics and subjective Bayesian statistics. A good general review of these schools can be found in Barnett (1982).

What is particularly important for our purposes about the subjective Bayesian view point is that it offers legitimacy and methods of calculation for dealing with opinions, in our case, opinions of medical experts. Modern Bayesian research concerns, among other topics, the elicitation of opinion in the form of probability distributions (Kadane et al. 1980), and this is the new technical tool being brought to bear on clinical trials. In an elicitation an expert is asked questions about his or her median for a dependent variable (the one being predicted) given specified values of the predictor variables (being used in the prediction). The answers to these questions, and other similar questions discussed later, are put into a computer, and they lead to a computer model of how the expert would answer any such questions. Thus Bayesian analysis allows us to study how experts are similar and different in their views, and also allows us to use these opinions for the benefit of patients without having physically to consult the expert about each patient.

1.6 PROPOSAL FOR A MORE ETHICAL METHOD FOR CLINICAL TRIALS

The possibilities opened by the subjective Bayesian technique led Sedransk and me (1980) to propose the following modification of the standard clinical trial.

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