Ethics and Clinical Trials: Some Neglected Issues

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Abstract

This paper considers five ethical issues arising in the conduct of clinical trials that have received little attention. However they are of prime importance in the implementation of clinical trials. The issues discussed are: (i) should per capita patient payment to physicians for participating in clinical trials be disclosed to the public; (ii) the conflicts in choosing a patient population (newly diagnosed or refractory to known beneficial treatment) in a Phase II trial; (iii) the notification to participating patients of the outcome of a trial before publication and/or newspaper publicity; (iv) the patients' right to know the identity of the treatment when participating in a trial where the treatment is masked; (v) the requirement by the FDA that confirmatory trials are necessary as part of the scientific evidence in support of a new drug application.

Introduction and Background

A large part of the literature discussing ethics in the context of clinical trials has been targeted at randomized clinical trials and the associated consent process. The papers by Bayne et al. (1990), Royall and the discussion (1991), Kiffman and Helfman (1992) and Pennerman (1991) discuss current perspectives. It is the purpose of this paper to discuss other ethical issues arising in the conduct of clinical trials, which are of prime concern, yet which appear to be neglected.

There are two well known definitions associated with the term "ethics." One definition refers to the rules or standards governing the conduct of a profession. The other definition refers to the moral quality of a course of action. In this paper, the reference to ethics will refer to the latter definition. However, in many instances writers on ethics have used these two definitions interchangeably.

It is worth noting that there is not a single absolute standard for ethical behavior. Society's view of ethical behavior, in the context of a course of action, changes over time. An action taken many years ago which appeared to be morally justified at that time, may not be so regarded today. Also, ethical behavior may vary with individuals, ethnic groups and countries. For example, in the United States it is generally accepted that a screening program for identifying asymptomatic individuals who are positive for the Human Immunodeficiency Virus (HIV) must have a counseling service available. Otherwise, many people would regard the program as "unethical." Should this same standard hold in other countries, where counselors may not be available? The letter by Gilles and Ware (1990) discusses the situation in Kenya and raises the issue, should such research be
Letter from the Editor

Dear Section Members,

I am very excited to announce the launch of the first issue of our new publication, the biopharmaceutical Agent. There are two main purposes for the report:

a) To disseminate information of relevance to Section members regarding meetings, conferences, books, and software (including reviews), educational opportunities (e.g., workshops, internships, short courses), etc.

b) To provide a vehicle for scientific interchange through letters, manuscripts, and discussions, as well as short, feature-length papers on interesting and relevant applied problems.

I encourage any and all input and contributions from Section members. Information concerning conferences, workshops, personal news, etc., is welcome. I am sure readers would enjoy brief contributions of non-technical papers, views and reviews, and reviews of software and books. Any suggestions for improvement of the report are also welcome.

I would like to thank several people who helped me put this issue together. First of all, I would like to thank Professor Zelen for his excellent paper, and all the discussions on the insightful comments and their timeliness. It would also like to thank Camilla Bochol for analyzing the results of the best presentation at ASA 1991 and the others who contributed to this issue. Additional thanks go to Bob Davis and Lionel Hyde, who have helped me consistently to edit and to Nima Miconi for designing the logo. Finally, I would like to thank Claydys Bagucho for her continued support and help on this project. Enjoy this issue and please contribute to the next one!

Avital Cnaan
Editor

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countries should also be referred to in the West when there is a joint collaboration.

The Wurtemberg Code was issued in 1947 during the Nuremberg War Crime Trials. It set forth the standards on how to judge Nazi physicians and scientists who conducted brutal experiments on concentration camp prisoners. The Wurtemberg Code put forth ten criteria to which physicians must comply when carrying out human experiments. These criteria have served as the prototype for many later codes; e.g., a code of ethics for human experimentation, termed the Declaration of Helsinki, was issued by the World Medical Association in Helsinki in 1964 and was later revised in 1975. In the United States there have been various guidelines on human experimentation issued by the various Departments and Agencies, the most notable being issued by the Department of Health and Human Services (HHS). In 1992 a uniform Federal Policy for the Protection of Human Subjects was adopted by 16 Federal departments and agencies. The U.S. Food and Drug Administration (FDA) also has issued guidelines that are similar in spirit to the uniform federal regulations but have some differences to reflect the Agency's regulatory authority. Guidelines have been issued in nearly all the developed countries of the world. Many hospitals and medical societies have issued guidelines on the ethics of human investigations. In general all have the underlying theme that 'concern for the interests of the subject must always prevail over the interest of science and society' (Declaration of Helsinki).

The guidelines for human experimentation in the United States have been heavily influenced by the Belmont Report which was issued in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This report reflected one of the charges in the Commission, e.g., to 'define the basic ethical principles that should underlie the conduct of biomedical and behavioral research.' This report did not make any specific recommendations for administrative action. However, it reflected the official policy of the Secretary of Health and Human Services. The basic ethical principles contained in the Belmont Report are centered on respect for persons, beneficence, and justice. "Respect for persons means that individuals have the right to make their own informed decisions. Individuals should be given the option of refusing treatment regardless of the consequences. Beneficence in the Belmont Report is interpreted to maximize possible benefits and minimize possible harm. It makes the investigator observe that the research is relevant and necessary and that what is harmful. In the process of obtaining this information, persons may be exposed to the risk of harm. "Justice" is interpreted to "frees the patient as a whole." The Belmont Report today still represents the basic ethical policy of the HHS even though it was published in 1979.

Bounty Trials

Many clinical trials are organized so that if a patient agrees to enter a clinical trial, the attending physician (or more precisely the private practice of the attending physician) will receive a sum of money on a per capita basis. We refer to these trials as bounty clinical trials. This is the traditional way in which industry supports clinical trials and is growing in popularity for NIH sponsored trials. For example, the National Cancer Institute has designated some cancer clinical trials as "high priority" and reimburses private institutions additional per capita funds for each patient entered on such trials. Occasionally, the funds are awarded in order to cover the extra costs incurred by the physician in collecting additional data required by the trial. In some instances the funding may be an incentive to help persuade the physician to enter patients, and there is controversy about setting the payment according to a cost accounting study of the necessary additional costs incurred. Actually, in many industry-sponsored studies, the data are usually collected by volunteers, employed by industry, who visit physician offices and abstract relevant data from the patient record. If a physician is in private
practice, the payment is clearly income. If the clinical investigator is employed by a research institution, these funds are used to support the research of the investigator’s unit and in some cases is used as a discretionary fund.

The exchange of funds on a per capita basis raises the issue of whether the clinical investigator may have been consciously or unconsciously influenced by the prospect of the payment of a “bounty.” It is not uncommon for industry and even government sponsored trials to add or even increase the payments to physicians for trials to which there is a problem accruing patients. The payments of such funds is generally unknown to the patient contemplating going on a trial. If the consuming patient was to later learn of the payment of such funds, it is certain to adversely affect the physician-patient relationship. One cannot dismiss the possibility that the physician may have been influenced by the bounty payment in persuading the patient to enter the clinical trial.

In order to avoid any misunderstandings, it is proposed that the payments be informed about the payment to the physician at his/her institution. Full disclosure of the payment should be part of the patient consent process. Disclosure is interpreted to mean the exact amount of funds and the intent for which these funds are to be used. It should be noted whether part of these funds are intended as an incentive to the physician, above and beyond the additional costs required for a patient to participate in the trial.

An alternative to the per capita payment is that support for patient participation in a trial be contracted on an aggregate basis. Payment is made in advance on the expectation that a fixed number of patients would be entered on a trial within a given time frame. This arrangement would avoid the per capita payment. It is less clear if this arrangement should be communicated to the patient in the consent process. One view is that in keeping with the spirit of full disclosure about financial arrangements the patients should be so informed. Another point of view is that since there is no payment on a per capita basis, the registration of the patient onto the trial does not initiate any transfer of funds.

Phase II Trials and Choice of Patient Population

The objective of Phase II trials is to determine if an experimental therapy has any beneficial therapeutic activity. An important consideration in planning these trials is the choice of the patient population. In some instances a beneficial therapy may exist. It may not be completely satisfactory, but nevertheless is believed to overcome the clinical problem arises in selecting the patient population. Should the population be those who have failed available beneficial therapies or should the choice be newly diagnosed patients?

Selecting newly diagnosed patients represents the best opportunity to evaluate the experimental therapy. However, it may deprive the patients of a potentially beneficial therapy. Alternatively, patients who have failed a potentially beneficial therapy, may be a poor patient population to evaluate the benefits of the experimental therapy. This situation presents a difficult quandary for the clinical investigator. In all cases it seems to be a clear cut answer to this problem.

The final decision on which population may depend on other factors associated with the beneficial therapy; e.g. cost, side effects, long-term benefit, access rate, etc.

Communication of Findings from a Clinical Trial

Clinical trials that find a beneficial therapy often make news, and are reported in the newspapers. Recent examples are the use of cytotoxic therapy to lengthen the disease free period for patients with node-negative breast cancer; 5-FU and levamisole therapy for the treatment of colon cancer; AZT as prophylactic therapy to delay the onset of AIDS for individuals who are positive for HIV.

Session Sponsored by the Biopharmaceutical Section at the 1992 ENAR Spring Meeting

Data Monitoring in the Pharmaceutical Regulatory Setting

Chair/Organizer: David DeMets, University of Wisconsin

There will be two talks and two discussions in this session.

The first talk will be given by Jack Warner, Corwin Drug, Inc. and Robert O'Neill from the FDA. The second discussion will be Thomas Pianta from the University of Washington and Lawrence Freedman from the NCI.

Dietary Quantification—Estimating a Moving Target

Chair/Organizer: Mikel Alkon, University of Arizona

There will be three talks in this session. They will be given by Lawrence Freedman from the NCI, Weston Lucas from the Ontario Workers' Compensation Board and Jasa McBane from the National Institute for Neurological Diseases and Stroke.

Estimation after Sequential Stopping

Organizer: Scott Emmons, University of Arizona

Session Chair: Philip Banks, University of Arizona

Three talks will be given by Koenigsmann, Klare from Harvard University, Karen Herbst and John Whitley from the University of Reading, and Scott Emmons and Philip Banks from the University of Arizona. The last talk will be the discussion.

Statistical Problems in Estimating HIV Seroreivalence

Chair/Organizer: John Kato, Centers for Disease Control

Three talks will be given by Michael Irons from the University of California at Berkeley, Donald Hunter from Johns Hopkins University, (with Alfred Mupo) and Vincent Carey from the National Cancer Institute. The discussion will be made by Morgen from the Centers for Disease Control.

reports discussing the use of streptomycin for the treatment of infections. The first two examples produced so called "clinical alerts" by the National Cancer Institute. These were clinical trials funded by the National Cancer Institute. Although no scientific papers were yet published, the National Cancer Institute called a major press conference and simultaneously sent a summary of the medical findings to a large number of selected physicians.

Should the patients who were participating in these trials be notified before there is widespread publicity about the trial? In the case of most dramatic results of the trial (e.g. negative outcomes), should there be patient notification before a scientific paper is published reporting the trial outcome? If one or more of the therapies under study are shown to be inferior, should the patients be notified of possible new treatment options?

A strong case should be made that the patients in the clinical trial and their attending physicians should be notified about the conclusions of the trial before a scientific paper is submitted. Certainly they should be notified before there is a public
annoucement. Furthermore, advice should be given on current and future treatment programs. This is especially important for patients who are or are receiving an inferior therapy.

Double Blind Trials

Some trials are conducted in double blind trials where both the patient and the examining physician are unaware of the actual treatment. Of course the patient has been notified in the context of the masking of the treatment. Suppose the patient decides that he/she wishes to learn the identity of the treatment. Is there an obligation that the patient be notified? The Belmont Report agreement that the patient should not be induced until after the research is concluded. If intervening the patient is "likely to impair the validity of the research."

However, suppose the patient decides to withdraw from the clinical trial. Patients always have the option of withdrawing from a clinical trial at any time. After withdrawing from the trial, should the patient be notified for breaking the blind be honored? Since the patient is no longer officially on the trial he/she would appear that full disclosure should be made to the patient by the responsible physician. A code can be made for learning the identity of the blinded treatment so that an off protocol treatment program can be planned for the patient. The off protocol treatment programs may be just as dependent on revealing the blinded treatment.

Food and Drug Administration (FDA) and Confirmatory Trials

The FDA issues guidelines to assist patient seeking the approval of a new drug. These guidelines are an amplification of the federal regulations which govern such approvals. The current guidelines state: "The requirement for well-controlled clinical investigations (phials) has been interpreted to mean that the effectiveness of a drug should be supported by more than well-controlled trials. Ordinarily, therefore, the clinical trials submitted in an application will not be regarded as adequate support of a claim unless they include studies by more than one independent investigator. There have, however, been instances in which a single particularly persuasive study has been accepted in support of a claim because the study was considered unacceptable on extraneous grounds. Such cases are unusual and an applicant seeking to invoke these exceptional circumstances must provide strong support for this position." (FDA, 1980, p. 19-20).

The requirements for a single trial to demonstrate efficacy are justified by the FDA as being "consistent with the general scientific demand for replicability." It is clear that there is a conflict between the welfare of the patient in which the physician does his/her best for the patient and the standards of scientific investigations which call for independent confirmation. The clinical trials writing should be regarded as being very different than a laboratory setting where independent replication of a finding does not exist serious ethical problems. The FDA guidelines acknowledge there is an ethical problem. However the defense of their position defies logic with one exception. The sole exception is an "equipoise" where the physician's goal is to show that (say) two treatments have identical benefits. Usually one treatment has FDA approval and the other is an experimental treatment seeking approval. Requiring confirmatory trials will not put patients at any adverse risk. Alternatively, if a trial does show an advantage of an experimental therapy compared to the standard treatment, then further confirmatory trials will result in some patients receiving a "inferior" treatment as judged by the scientific evidence at that time.

In practice the FDA guidelines are often satisfied by planning several independent trials in parallel, so that the outcomes are known as approximately the same time. Sometimes, the confirmatory trials are made of different patients populations as at a different dose level. Nevertheless the entire process does not seem defendable. It would be an "awkward" problem for the physician is notified that the trial is a confirmatory one where an external trial showed the superiority of the drug. It is of some concern how the patient's current process is carried out when the physician is entitled to sell the patients that scientific evidence is available demonstrating the superiority of a treatment.

It is strongly recommended that the FDA guidelines be modified so that drugs may be approved without the necessity of confirmatory studies. However the FDA should require post-marketing studies which confirm the efficacy of the drug as a condition of approval. Confirmatory clinical trials would still be required for equivalent drug trials.

Ethical Omniscience

The continuing debate on the ethics associated with clinical trials often mixes the lawsuit of conscientious. Several surveys serve to illustrate this point. At the present time the AIDS Clinical Trials Group (ACTG), a federally funded group of investigators carrying out clinical trials on therapists to treat AIDS, is placing a trial on pregnant women who are HIV positive. It is estimated the 15-20%
of the infants will eventually be diagnosed as asymptomatic by virtue of transmission from the mother. The intent of the trial is to determine if AZT can reduce the transmission rate. The plan of the trial is to randomly allocate the women into two groups. One group would receive a placebo and the other group would receive AZT during pregnancy. At birth, infants from women in the treated group, would also receive AZT. The Office for Protection from Research Risks (OFPR), NHL, has mandated that it is necessary to obtain consent from both the mother and father (if available) of the unborn child. In the event the father declines to give consent, the pregnant woman would, in theory, be denied an active therapy which has been shown to delay the onset of AIDS. This consent process must be viewed against the background that in most states women have the legal right to obtain an abortion without the consent of the father. This author wrote the OFPR inquiring if there were any special studies or panels convened to study the issue of consent. I was informed that there were none and that the decision to obtain the father’s consent follows the Code of Federal Regulations (45 CFR 46) entitled “Protection of Human Subjects.” Paragraph 46.208 of the Code of Federal Regulations does indeed specifically require both the mother and father to give their informed consent unless “(1) his identity or whereabouts cannot be reasonably ascertained, (2) he is not reasonably available or (3) the pregnancy resulted from rape.” However, the issue of requiring informed consent from both the father and mother for this study is not at all clear cut. Paragraph 46.408 (b) does enable an Institutional Review Board (IRB) to allow the consent of only one parent when the research involves “greater than minimal risk but presenting the prospect of direct benefit to the individual subjects” (46.405). The OFPR decision has overruled any flexibility on this matter by IRBs.

Angell (1990), in an editorial in the New England Journal of Medicine, stated that the “Journal will not publish reports of unproven therapeutic or scientific merit... The approval of the institutions, review board (when there is one) and the informed consent of the research subjects are necessary but not sufficient conditions.” This has been termed “ethical omniscience” by Greene (1990). He writes, “An editor who views decisions reached by local review boards as the precarious position of claiming to have insight into ethical matters that is superior to that of all others and to be justified in unilaterally rejecting decisions made by duly constituted review boards. The validity of such claims is dubious, indeed, although examples of such judgment and arrogance in research review...” The comments on the potential benefits to the children involved in the trial are also raised. He states the potential question of why review boards should be established in the first place if their decisions can be easily overturned by someone far removed from the scene who claims ethical omniscience.” The OFPR and editors of journals are in a certain sense omniscient. They are not subjected to the changing ethical problems in human investigations which are constantly challenging our society. Special or unusual situations should automatically generate a special study group to decide on the ethical issue. Otherwise one is reminded of the vitriol, “How does the government, editor, etc. make decisions? The same way a gerril makes love! How does a gorilla make love?—Any way it wants to.”

References

reflection will then be a chance of dealing with the questions he raises (Levine, 1967).

A byte of a problem comes in the opening paragraphs where a strange understanding of ethics is presented. He offers a simple, traditional statement of descriptive cultural relations (the view that different cultures at different times bear different moral postures). He uses this to support the claim that "there is a single absolute standard for ethics any more than it follows from the fact that different cultures at different times have had different conceptions of the physical universe, that there are no more or less right accounts. It may be, for example, that two societies adopt different positions regarding the requirement of counseling and still agree on the same general moral rule such as, "Prove counseling whatever it is available and affordable."

Fortunately, Dr. Zelen's more specific observations about the ethics of clinical trials are far more challenging. I would like to suggest that if the principle of respect for persons he refers to (is fully developed it provides a criterion framework for addressing the questions he raises. If, and only if, patients (and non-patient subjects) are made full partners in the research process and given the opportunity to be active participants and emotionally informed decision makers, will the answers to these questions emerge.

Informed people would agree to be in a clinical trial only when they are relatively indifferent to the treatment options. They are at one near what I have called the "indifferent point," at that point the whole hypothesis is plausible for them (taking into account their subjective assessment of the potential benefits and risks). At that point (and only at that point) it is ethical to randomize. (This patient will not care which arm he or she enters.) Subjects must be given whatever it takes to make such choices. That, I believe, provides a framework for dealing with most of Dr. Zelen's questions.

In assessing how groups of patients are in the indifferent points for the various study options, it is not useful to ask them to be indifferent about what the doctors or the doctors about them. However, it is interesting that at the same time feeling particularly attracted to the possible benefits of the new therapy. For ethical purposes, some of these groups may be acceptable, others in both groups may not be.

So also this framework provides a basis for dealing with the question of consent and findings. If patients have a moral right to be told what they would reasonably want to know, then

References
Discussion

Stanley S. Schor
Merrick & Co., Inc. (retired)

I was extremely pleased to see a paper addressing some ethical issues which have bothered me for some time, especially in my last position in which I was responsible for thousands of clinical trials being undertaken all over the world. I would like to discuss each of the four issues raised by Dr. Zelen and then raise one of my own. Since I am limited in space I will mention only the most important points.

In addition to the problems Dr. Zelen raised about trials in which the investigator is paid on a per capita basis or even on an aggregate basis, there are other concerns. The exchange of funds may very well influence the investigator in other ways than those mentioned by Dr. Zelen. If the investigator agrees to complete his study by a certain date and patient recruitment is slower than anticipated, he or she might be tempted to start admittance patients who do not meet the protocol requirements in order to secure his payment. This would introduce a bias which could in some cases render the study useless and the experimentation on these patients wasted.

In either case, per capita or aggregate, the patient should be informed. I would go even further. Not only should the patient be informed that his or her physician is being paid, but the patient should be given something for his or her willingness to participate. After all, he or she is taking a chance on getting a placebo or possibly a worthless treatment and should be compensated for assuming this risk. Why should the investigator be compensated, be given the opportunity of doing research, probably get a publication and some fame, while the patient assumes all the risks but gets nothing?

As far as the choice of patient population is concerned I think Dr. Zelen has covered it nicely in terms of newly diagnosed versus treatment failures. But there are other problems.

Ideally the patient population should be representative of the diseased population for all important characteristics (age, sex, etc.). But ethically this may not be possible. How close can one come to the real target population without the patient assuming unwanted risks? Most clinical trials are performed on people who have only the disease to be treated and no other.

Yet more people with that disease have other complicating problems which exclude them from the trial but which may affect their response to the treatment.

I agree that patients should be informed of the results of the study before any other scientific papers appear. They volunteered for the study and the least that one can do is to notify them of the results and current and future treatment options. I do not think it is necessary to wait for a confirming study or for peer review before informing the patient.

The patient should not be told which treatment he or she is on while in the study. But once the patient is dropped from the study for any reason, he or she must be told which treatment was being administered so that an appropriate regimen can be selected.

I could write a book on the problems encountered with the FDA requirements of two independent positive studies. Not even the people at the FDA agree on what constitutes a positive confirming study. Suppose there are two important endpoints in a trial.

Does the experimental treatment have to be significantly better than the control for both endpoints in both studies? How about all four in the right direction but only three statistically significant? Or all four in the right direction but only two significant, the same one in each study? Or different ones in each study?

Suppose there are more than two endpoints. Some FDA reviewers require the same endpoint to be statistically significantly better in both studies while others feel it is O.K. if some endpoints are significant in the first and others in the second as long as they are important endpoints and the others are in the right direction. It seems unethical to me to withhold a probably good treatment until two studies yield statistical significance in exactly the same endpoints.

And what does the FDA mean by two "independent" studies? Must there be different investigators, different clinics, different patients, different monitors—just what is meant by "independent"? Even the FDA people cannot agree.

Then there is the question of strategy. Should a drug company do three studies at 80% power in order to get out two of three positive, or two studies at 90% power to have an 80% chance of having them both be positive? In both uses more patients must be experimentally on than if 80% power is used in both and the FDA is willing to accept one significantly positive and one with results in the right direction.

Finally, I would like to say something about concern for the interests of the subject must always prevail over the interest of science and society (Declaration of Helsinki). If this is to be followed, and I, of course, think it should, then for any disease for which there is already a known treatment, any new and possibly better treatment should not be tested against a placebo.

This, however, flies in the face of current FDA requirements. If there is a new antihypertensive drug or a new NSAID, for example, it must be tested against and be demonstrated to be better than a placebo, not equal to or better than any of the existing drugs, in order for it to be approved for marketing. This requirement I found really bothersome in my tenure at Merrick and Co., not only because some patients are given the placebo when a beneficial treatment is available, but also for the following reason. If a new treatment is shown to be better than a placebo, but, unknown to the FDA or the drug company, it is worse than an already existing treatment, it may very well be approved. At any rate, my hat is off to Dr. Zelen for raising these very important issues.

Discussion

Richard M. Royall
Johns Hopkins University

Although the five issues that Professor Zelen highlights have not received much explicit attention in the literature he cites, which is targeted at randomized clinical trials and the associated consent process, it seems to me that the consent process is critical in the first four examples and the viewing those in the light of informed consent goes a long way towards clarifying them.

The consent process implies that the subjects in a clinical trial must be fully informed of every aspect of the trial that they might reasonably be expected to consider relevant to their decision on participation. Since most patients would surely consider it serious if the physician or hospital will receive a cash payment if they agree to take part in a study, in Professor Zelen's first example ("bounty trials") his conclusion is unavoidable: "Full disclosure of the payment should be part of the patient consent process."

Informed consent requirements in general medical practice represent the physician's responsibility for candor and the patient's ultimate right to reject the physician's advice.
Organized and summarized by Nick Teoh

The Biopharmaceutical Section had several well-attended roundtable luncheons during the 1401 Joint Statistical Meetings. In addition to having a good lunch, most members were able to interact with the discussion leaders and gain some understanding of various aspects of statistical research that are of current interest in the pharmaceutical industry. Since several of the discussion leaders were involved in various biopharmaceutical work groups, they also had the opportunity to make a report and, if interested, formally join the work group as a participating member. Alternatively, members could also solicit interested participants to form a new work group. Such interest was the case with a new work group led by Christy Chang-Stein that will be focusing on dose-ranging study designs. This new group is currently comprised of eight members (from seven different companies) of the luncheon. However, anyone else is invited to register in similar lines of new work in still welcome to join this and other work groups at your own convenience at the luncheon. Interested members of the pharmaceutical section would like to obtain additional information on the various work groups in which they wish to organize new work groups can meet Nick Teoh at Abbott Laboratories, 8A1-A605, Abbott Park, III, 60064. Tel: (708) 737-4421.

As a recap of some of the discussions that took place during the luncheon, the following are synopses provided by several of the discussion leaders.

Dose-Ranging Studies: Paralleling Design vs. Titration Design

Christy Chang-Stein

This was a well-attended luncheon with participants from several different pharmaceutical companies. The participants were concerned about the design of dose-ranging trials as well as ideas on the ideal strategy to adopt for such trials. The discussion centered on an enthusiastic note with a positive request by the participants that a new biopharmaceutical work group be organized for further research on this topic. The proposed function of the new work group will be to focus on identifying the role of parallel designs and titration designs in drug development, and more generally, on investigating the optimal strategy for determining dose-response relationships. In particular, the work group will attempt to address several issues concerning:

- Current practices regarding dose-ranging studies in the pharmaceutical industry
- Relevant literature pertaining to this subject
- Strategies on how dose-ranging designs can be best utilized under various experimental scenarios

A letter outlining the plan for this work group has been circulated to the participants for additional input. Interested members of this section are prepared to "fill up their sleeves and do some research work" on this topic should contact Christy Chang-Stein at The Upjohn Company (Tel: 616) 385-7872.

More synopses can be found on the following pages.
Discussion

I. Craig Henderson
Dana-Farber Cancer Institute

I am pleased to have the opportunity to comment on Professor Zelen's paper on "Ethics and Clinical Trials: Some Neglected Issues." As usual, they are provocative. However, I wish to iterate my disagreement with Dr. Zelen on several points.

First, on the inclusion of information as the informed consent regarding so-called "benefts" for patients entered into clinical trials. Dr. Zelen, reasoning is flawed, as long as it ignores all other aspects of clinical practice. However, it cannot be assumed that an investigator has a bias in recommending a protocol and that non-investigator physicians have no bias in recommending a variety of other therapies. I would be perfectly happy to include information regarding the support of clinical research in informed consent documents if in-vitro investigator physicians were required to provide their patients with information on the financial value to the physician of various treatment options under consideration by the patient. If I had my choice between providing no information at all or providing full disclosure in both settings, I would easily choose the latter.

In Dr. Zelen's discussion of the choice of patients for Phase II trials, he seems to me to have given inadequate consideration to two possibilities. First, the so-called "standard" therapy may, in fact, have little more than placebo value because it affects neither endpoints without altering the patient's quality of life or survival. Second, there is a large number of therapeutic in-vitro in all areas of medicine and especially cancer medicine. Moreover, other areas of science, "medicine does not frequently devote a therapy "effective" unless there is another alternative. This is especially true in the United States. For example, it was clear for many years that the radical mastectomy provided little, if any, survival benefit. Nonetheless, this continued to be the choice of treatment for most patients until an equally radical but somewhat more plausible treatment could be therapeutically conducted radiotherapy. The therapy also has a very little impact on patient survival, and it is defendable whether all patient "lives" are improved by having hemipectectomy followed by immediate radiotherapy rather than hemipectectomy with delayed radiotherapy given only to those patients who develop a second cancer within the breast. Radical local therapy for breast cancer has been used for all of the past century, and, a solid argument could be made that most treated individuals have been more harmed than benefited by the therapies employed as "standard." A second aspect of this which Dr. Zelen has not considered (or at least discussed) is the possibility that the standard therapy might be equally effective in achieving the same nongrade survival, whether given early or late, while the new therapy, if effective, might be of benefit to the patient only if given early. It is difficult to prove this point, but most clinicians have observed that new drugs employed following the patient's development of resistance to standard treatment are not only unlikely to induce remissions, they are also likely to induce additional toxicity during the patient's last days. The major benefit to individual patients from using a new therapy is the "hope" that it engenders. Who is to say that this particular benefit is better delivered in the early stages of the patient's disease when the patient has relatively few symptoms but feels uncomfortable doing nothing, or late in the patient's course when suffering is maximal and all active measures have been tried?

References


1991 Biopharmaceutical Work Group

Randomized Concentration-Controlled Trials (RCTC)

Liangh Yuh

The focus of the discussion, which was led by Liangh Yuh and Lilly Samahanam, was centered on utilizing pharmokinetic data to choose an optimal dose or drug concentration, instead of randomizing patients into different dose levels. Peck and Redman (1991), and Starrenbaum and Peck (in press) had suggested that patients should be randomized into different predetermined levels of average plasma concentration. The target concentration for each patient is to be achieved by using an individualized blood concentration-controlled dosing scheme. This approach is based on the assumption that the blood drug concentration is proportional to the drug concentration at the site of action. Clearly, RCTC's are more efficient, then conventional dose-ranging designs if there is a significant pharmokinetic-pharmodynamic correlation, some of the topics that were discussed among this group of outmoded luncheon participants included:

- The role of the placebo treatment group in RCTC's.
- Approaches for handling drug compounds that lack significant pharmacokinetic/pharmacodynamic correlations.
- Approaches for handling drug compounds that possess multiple active metabolites.
- Use of the blood level as a covariable.
- Advantages and disadvantages of RCTC's
- Alternative models (e.g., measurement error models).
- Comparison of RCTC's with other designs.

In addition, the role of RCTC's in Phase III of drug development was also discussed. The participants included representatives from the government, industry, and contract research organizations (CROs). There was a general consensus that RCTC's could be particularly useful for analyzing drugs with narrow therapeutic windows.

Population Pharmacokinetic Modeling Work Group

Ken Kowalski/Liangh Yuh

Members of this group met during the Joint Meetings in order to plan their goals for 1991-1992. One of the immediate goals of the group is to assemble an extensive bibliography of references consulted with this research area. The bibliography will contain references for each of several categories, including theory, application, software, and others. In addition, the group is considering the publication of a review paper in early 1992 in a suitable scientific journal depending on the target audience. There are also long-term goals to assemble a series of real data sets containing the necessary information to use in examples of applications of various methodologies, as well as plans to conduct simulation studies to evaluate current available methods of analysis. The interested readers of this section who wish to participate in the research activities of this work group may contact Liangh Yuh at Pfizer-Denov (Tel: [313] 996-9834).

More synopses can be found on the following page.
1991 Biopharmaceutical Work Groups (continued)

Statistical Education of Nonstatistical Personnel in Industry

Tom Bradstreet

Most of the participants in this lecture taught courses for engineers and medical research personnel. Their current course philosophies and contents included statistical reasoning, statistical concepts, experimental design, data analysis, use of statistical software, and proper interpretation of results. Based upon their prior teaching experiences and proposed improvements for the future, the participants were able to construct a list of guidelines for designing and teaching a statistics course for nonstatisticians in industry. Some of the do's and don'ts that they suggested included:

Do:
- Teach statistical concepts first, then methods.
- Train "para-statisticians" or clients who are able to understand and perform simple analyses but who also know when to seek professional assistance for complex problems.
- Provide instruction that is immediately applicable to the client's subject matter area.
- Learn the client's subject matter and local terminology before designing teaching a course.
- Connect statistical concepts and methods to user-friendly software.
- Teach theory, but be avoidable, rely the theory to a concrete subject matter application.
- Fail to clearly define the limitations of each statistical method.

Don't:
- Teach theory, but be avoidable, rely the theory to a concrete subject matter application.
- Fail to clearly define the limitations of each statistical method.

Statistical Literacy: Innovative Ways to Introduce Statistical Concepts in Local Schools

Mike Boyd

The focus of the lecture took was presentations for grades 8-12 by biopharmaceutical statisticians. In addition, some of the attendees for teaching statistics that are available through the ASS and the Qualitative Literacy (QL) programs were also discussed. Some of the many courses ideas shared included performing a randomized clinical trial in the classroom and analyzing the outcomes; designing an exercise to illustrate the project team concept and the data, how concept asking, children what they want to when they grow up, and then discussing how statistics is used in that field; and serving pizzaioli times in enabling popcorn and seeing how that affects the number of unpopped popcorn kernels. The participants also suggested tips and strategies including: don't try to do too much; hold the students' attention and keep things moving; have them partner; have two or three adults; and most of all have fun!

Participants of the lecture agreed that broad presentations can make a strong impression on school children and are definitely worthwhile, and that statisticians can make a long-range impact on elementary and secondary education by participating in QL workshops. It was suggested that teachers should try to come up with generic problems sets that kindergartners through adults can order. The participants also expressed the hope that companies with summer internship programs will consider using teachers as interns.

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I fully concur with Dr. Zelen's comments regarding the communication of findings from clinical trials, but would go a little further than he has. Shouldn't physicians on the inferior arm of a randomized trial be offered the possibility of crossover after that arm has been shown to be inferior? For example, in CALGB 8541, a study in which patients were randomized to three different doses of adjuvant chemotherapy, we immediately offered higher doses of therapy to all patients who were still receiving drug when the observation was made (and long before publication) that higher drug doses were superior. What would have been the effect of such a requirement on the publication of the NSABP, intergroup, and international adjuvant therapy trials in node-negative patients? As physicians/investigators, we frequently argue that a therapy will be more effective for patients on the inferior arm if employed after the trial has closed to further accrual. This is a self-serving argument, since we really have little or no evidence to support this contention. In the case of using adjuvant chemotherapy, the international trial suggests that at least a month's delay in the initiation of therapy does not compromise results at all. In actual practice, physicians treat asymptomatic metastatic disease described by the deviation of a marker (e.g., CEA or CA15-3) on the assumption that all "early" treatment is better than "late" treatment. Given this assumption, then, why is it not reasonable to treat a patient with adjuvant therapy who is 6-12 months out from diagnosis once it has been shown that she "missed out" on the benefits from early therapy?

Finally, the section on the FDA requirements for confirmatory trials does not seem to address the issue of false positive results. Dr. Zelen once wrote a paper suggesting the approximately half of all published trial results represent true positives, and I believe that we could easily find many examples in the history of medicine in which such false positives have yielded misery for thousands or even millions of patients over decades or centuries. Probably the example of the medical-maternal syndrome applies here, as well. To me the solution to the problem is not to lower the standards by approving drugs on the base of a single trial, but rather to rest that drug development be based on more careful long-term planning.

Practically, this means limiting uncontrolled Phase II trials to the minimum number of patients necessary to justify an appropriate Phase III trial and the initiation of several Phase III studies at one time. I think that the use of multiple dose chemotherapy and autologous bone marrow transplant is a good example of the appropriate use and acceptance of prolonged Phase II trials (as well as the inappropriate publication of premature results without information of the importance of additional studies—survival).

Discussion

Benjamin Freedman

McGill University

Not long ago, the only financial issues dealt with by those sitting on the ethics of clinical trials concerned payment to subjects. Who should be reimbursed? When is it excessive (Macklin, 1981; Ackerman, 1980)? It is of course easier to raise the question when it concerns the propriety of paying another, somewhat less so, when one's own financial arrangements are called into question.

It is therefore not surprising that discussion of the ethics of 1

1The author gratefully acknowledges support provided in preparing this article by grant MOP-931-003, awarded by the Social Sciences and Humanities Research Council of Canada's program in applied ethics.
paying investigators for participation in research has been space. Professor Zelen is to be congratulated for courage and perseverance in raising the issue of reimbursement methods for investigators. But the questions raised are numerous, and highlight important and noble ethical issues. In this brief note, I would like to point out some of these questions.

Space forbids a responsible examination of Dr. Zelen's major recommendation, that part of the informed consent of subjects disclosing financial arrangements. I would suggest though that these questions other than direct costs asking. The ethics of classical trials involve a delicate balance between the claims of scientific medicine and those of ill persons. This balance must be expressed at the outset of a trial, when a hypothesis worth investigation is identified; during the progress of a trial, when decisions concerning the management of patients are made; and when decisions are made to bring a trial to closure, and an analysis of its findings is attempted. Payment for participating in a trial, and other professional inducements, may subtly distort the balance at any one of these stages, for example, by leading an investigator to exaggerate his or her own success rates, time, in studying a trivial problem; by enrolling patients who may be endangered by their participation in a trial, or by maintaining them on protocol restrictions past the point of prudence, by leading an investigator to make inflated and unsubstantiated claims on behalf of the trial.

Philosophical analysis of any issue proceeds by a process of repeated and refined distinctions. At first step in examining this issue, we may distinguish between issues arising from the source of payment, the form in which payments are calculated and made, and the determination of payment.

Sources

University researchers and members of research ethics committees are often between 1989 and 1992, has been closely and sceptically at studies funded by drug companies. As Dr. Zelen points out, however, similarly troubling financial arrangements—e.g., 'booby' payments for recruiting subjects—may be found in research funded by NIH, and other peer-reviewed sources.

Indeed, non-profit sponsors of trials may raise more complicated issues than drug companies themselves. A functional analysis of inducement must begin with the premise that a medical scientist's behavior is influenced by many factors. Money is not the sole, nor necessarily the most prominent, inducement for pursuing studies as an investigator and recruiting subjects. If we are justified in questioning the propriety of inducements for investigator participation, and considering such reforms as discouraging them in some circumstances, we must proceed upon the basis of a broad, accurate and fair inventory of research inducements. Simply lumping together as a co-investigator in a major trial funded by NIH may be more professionally meaningful to the investigator than any payment likely to be offered.

It is no good enough to focus upon payment, and to fail to consider other forms of professional inducement purely on the grounds that payment is questionable. Those other factors can be questioned as well; indeed, they commonly are, in institutional policies promoting or endorsing.

Are there other troubling sources of payment? If the only source of concern is investigators' payments were cost of deception of research subjects, it would follow that studies that are paid for by subjects themselves (as in some institutional arrangements for investigative center treatments, e.g., biological modifications) would not be an object of concern. If, to the contrary, any arrangements that distort for ethical balance of the planning and conduct of trials to generate patent-based research little qualifies. One bottom line question for these arrangements is: Will payment distort the researcher's scientific or clinical

FDA CORNER

We would like to call Dr. Zelen's attention to the perspective, thoughts, interesting issues of advisory committees, etc. in order to open this corner. We begin with a paper written by Dr. Yu-Min Seg and Elder (author's termination).

My Life at FDA

Type-I error is what I care, Active control is what I care, Simply sit in what I care, Hypothetical I hard to get. I don't look back to pay a price. Unfavorable means reliable paid. Placebo control is what I love. Bad studies are hard to serve. Multiple endpoints make adjustments, stopping rules must be properly set. Multicenter produces interaction. Good studies require careful randomization. Efficiency is not all I care. Safety may be what I care. Confidentiality is what I need. Power may be hard to get.

Efficiency is not all I care. Safety may be what I care. Confidentiality is what I need. Power may be hard to get.

Judgment, in his or her plan for intervening in ways that will further medical science while not compromising the patient's medical judgment? In examining the sources of payments for investigators, we must ask whether the agenda of the funding party is likely to dominate and distort the judgment of the investigator—and, what can be done to forestall that possibility.

Forms of Payment

What is most troubling about arrangements for paying investigators? Is it the amount that is paid? The means in which it is calculated? The manner in which researchers qualify for payment? The answer is, disappointingly, "It depends." Each of these can contribute to an index of ethical suspicion regarding a trial, but none is conclusive in and of itself.

Dr. Zelen notes more disturbed by the exorbitant value of research reimbursement than by the sheer amount that is involved. Calculations of reimbursement are commonly done very roughly, with little relationship between how much it costs an investigator to run a trial and how much he or she will be paid to do the trial, and Dr. Zelen is clearly concerned that this loose method of calculation is designed to allow the researcher to pocket a profit for enrolling subjects. It has been claimed that these rough calculations often work so as to dampen the enthusiasm of researchers, rather than to their advantage, leading to a net cost rather than profit per patient (Levin, 1988). The own (united) experience in reviewing
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towards subjects. And rather than privileging some forms of payment—e.g., that which will be directed towards a discretionary research fund to the department, rather than to the pockets of investigators—we need to similarly value what functional difference payment will make to the "benefits and conduits of those in whom a patient's fate is engineered.

In conclusion: The problem of investigator's payment reveals again fundamental issues of interdisciplinarity problems. What is "payment," and are other professions involved in these problems? Are some funding sources, or funding arrangements, particularly likely to get the ethical conditions correct? There are issues that research ethics committees need to examine, soberly and fruitfully. A good first step to this would be for committees to require full financial disclosure to them when reviewing studies, and a necessary second step would have committees share their experiences and approaches in print, rather than in hallway conversations.

References


Discussion

Susan Ellenberg

National Institute of Allergy and Infectious Diseases

Professor Zelen has written a provocative paper exploring a number of aspects of clinical trials that may raise ethical questions but that have not been widely discussed. He makes the very important point that there are no "absolute" ethical standards; that what is acceptable to individuals and groups varies greatly, both with geography and with time. As Dr. Zelen notes, this variation may lead to difficulties problems in conducting multicenter trials even within our own country. We must deal with continuing shifts in the "consensus" view of what is ethical.

I can't agree with Dr. Zelen's distinction between ethics as standards of professional conduct, and ethics as the moral quality of a course of action. To my mind, standards of conduct are ultimately founded on moral principles, so the utility of drawing this distinction is unclear to me. But if we do agree that most of the issues he raises present ethical issues that are worthwhile discussing.

The practice of per-person reimbursement to physicians for clinical trial accrual has been extensively discussed, both from the ethical perspective as well as the perspective of finding the most efficient way to conduct clinical trials. That said, of course, be some provision for payment of research costs—and these needs to be some incentive system if we believe that clinical trials, particularly of potential life-saving therapies, should be carried out in the most rapid and efficient way possible. Trial sponsors, especially the federal government, would be properly criticized if the provision of research funds to clinical investigators was entirely independent of how the researches' ability and willingness to enter patients on trials. One might argue that a system that failed to ensure that a trial of a promising new agent was completed as quickly as possible was behaving in an unethical manner.
It should be noted that money is not the only type of "bounty" made available to trial participants. Some trials groups have a policy of allowing the order of authorship according to the number of patients entered, and/or excluding some participants from authorship if the number of patients they entered was insufficient. Investigators who repeatedly enter large numbers of patients are likely to become chauffeurs of trials and attain a higher level of visibility in their profession. Should such arrangements, or likely consequences, also be revealed on center forms?

The issue of appropriate populations for early (presumably uncontrolled) trials of experimental agents may be viewed differently in different disease areas. Certainly for diseases in which therapy is short-term and there are not likely to be major adverse consequences to delaying a known effective treatment, it may be acceptable to offer a patient an experimental agent that might be worse (or better) than the standard therapy, as long as the patient is clearly informed. For cancer trials, the standard practice for NCI-sponsored trials is that among patients with no known effective therapy, the population most likely to exhibit benefit should be selected for these early trials. For example, patients with intractable cancer who had not yet received a platinum-based regimen should not be entered onto an uncontrolled trial of a new agent. For patients with pancreatic cancer, however, newly diagnosed patients should be the target group, since they are more likely to exhibit response to an effective agent and there is no known effective therapy for this disease. (Most investigators would not regard a drug "effective" that induced minimal tumor reductions in a small fraction of patients without any survival advantage.) In AIDS, there has been a strong urgency for patients themselves to demand access to new therapies, whether or not a beneficial therapy is available. Despite the fact that AIDS has been clearly demonstrated to be a long disease, many newly diagnosed patients, anxious to avoid its side effects, prefer to seek out alternative therapies. It is an interesting dilemma for physicians who may believe patients will benefit from an available drug when confronted with patients who would prefer to try something new that might be more effective and/or less toxic, but might also be ineffective or even harmful.

With randomized double-blind trials, I don't believe that a patient's withdrawal from a trial releases him from his agreement to forego knowledge of the treatment assignment, any more than it releases the investigator from his agreement to maintain the confidentiality of the data. I do believe, however, that trials must be reasonably designed to ensure the availability of optimal therapeutic options for patients who fail the assigned therapy. AIDS trials that are double-blind are designed with second-line alternatives (appropriate to the initially assigned therapy) built in. Patients who withdraw from a trial prior to failure would still have the opportunity to benefit from any of the trial therapies, including the one assigned in the trial, so that breaking the blind would not seem to be mandatory in such cases. In the unusual circumstance in which optimal therapy for a patient cannot be selected without knowledge of treatment received in a double-blind trial, I would certainly agree that the patient should know about the sponsor's interest in maintaining the blind.

Dr. Zelen takes issue with the Food and Drug Administration's policy requiring two or more well-controlled trials to establish efficacy of a new agent. The FDA is itself somewhat conflicted about this policy, which, as Dr. Zelen notes, is intended with some flexibility. This issue is part and parcel of the overall concerns raised over the decades of the ethical status of randomized trials in general. How long should an individual trial continue? Should we stop a trial before the power accrual and follow-up is complete if the overall response rate is lower than anticipated? One would say that as soon as any novel emerges, it becomes unethical to continue randomization. It appears to me that the generally accepted requirements for demonstration of efficacy—that the study results be inconsistent with the null hypothesis of no treatment effect at the 0.05 level of significance—is no less arbitrary than the FDA policy. Dr. Zelen cites. Why not significance levels of .10 or .20? On the other hand, it has been argued that we should make our standards considerably more stringent for individual trials, requiring three rather than two standard deviations for statistical significance (Petos, 1987). There is clearly a continuum of magnitude of interest, and the FDA policy may be too conservative in Dr. Zelen's opinion, but Dr. Zelen and others have provided a rationale for such conservation in many circumstances (Zelen, et al., 1980; Steup, et al., 1979; Simon, 1982). They have shown that when only a small proportion of drugs entering clinical trials are truly effective, the "false positive" rate may be much greater than the 0.05 one might expect. It is a simple consequence of Bayes' theorem that, if only 20% of new drugs are truly effective, a new drug meeting the "p<.05" test in a clinical trial has only 80% probability of being truly effective, if only 10% of drugs tested are truly effective, the falsenegative rate is 64%, and a 1% one implies that a drug found effective in a clinical trial has only 14% chance of being truly effective. (These calculations are based on the assumption of 50% power in each trial. If trials are underpowered, the false positive rates will be higher.) Dr. Zelen's position here that confirmatory trials may be unethical is surprising, given that he has previously taken the position that confirmatory trials should always be done when feasible (Zelen, 1983).

Finally, I believe the concerns Dr. Zelen raises about the respective roles of local review boards, the federal government and editors of medical journals in determining what constitutes ethical research are interesting and important. It is certainly arguable that those who sponsor research, and those who publish it, have an legitimate an interest in the ethics of the research as those who physically take part in the research. This view implies the need to build wide consensus about new and difficult ethical issues, a process requiring the types of public airing of different perspectives that Dr. Zelen cites.

References

Rejoiner
Marvin Zelen
Harvard School of Public Health

I wish to thank all of the discussants for their comments on my paper. They all agree that the problems raised require more serious attention. In addition, several have amplified ethical concerns which certainly require further discussion. In these remarks, I wish to briefly comment on some of the issues raised by the discussants. My comments will be in inverse alphabetical order of the discussants.

Professor Vatch has authored a "cholstered book" (Vatch, 1981) on medical ethics which has, as one of its themes, that the resolution of ethical issues and conflicts can be done on the basis...
of a coherent theory. In other words, given a core of ethical theory, specific ethical problems may be resolved by consideration and application of the core theory. In principle this could lead us out of the current "chaotic state" of medical ethics. I believe the principal disagreement between Professor Veatch and myself on this issue is that my view of medical ethics is related to the practice whereas his comment on a "core ethical vantage point" is a deniable idea. History illustrates the changing nature of cultural pluralism. One need only review the evolving Hippocratic tradition as described in Professor Veatch's book to strengthen my view. He writes, "Only gradually will we begin to see how base and conventional this Hippocratic ethic is and how strange it would be if medical people, whether operating out of the religious or secular moral framework, were to revive the ethic of the Pythagorean-Hippocratic code." 

Professor Veatch remarks that rational people would agree to participate in a clinical trial when they are informed to participate. There is no dispute about this aspect. However, its implications is difficult. The physician's selection of information to communicate to the patient and the patient's comprehension are not ideal. Professor Royall also addresses the issue of "practical problems of education and communication so that the patient understands enough to make a free and informed choice." A further complication is that the physician, and, in many instances, the pharmacy, may underdose with free information communication. These same issues arise in participation of Phase II and confirmatory trials.

Dr. Scher has a wealth of experience in dealing with the FDA. From an industry perspective, there are very few individuals who can match his record. He notes that there is considerable disagreement within the FDA on the need and practice to have at least two independent trials in order to have drug approval. In fact one need only cite the recent FDA action for the approval of the agent DDI for the treatment of AIDS. On October 9, 1991, the FDA finally gave drug approval. The independent clinical trials were completed showing that DDI prolonged survival. Approval was based on laboratory data showing that DDI raised the CD4 count of DDI-treated AIDS patients. The clinical trials evaluating AIDS are yet to be completed.

There is no doubt that the FDA is exhibiting considerable flexibility in drug approval, by giving approval without a single completed trial. If this is to be the future policy of the FDA, it is essential that post-marketing surveillance be provided to the patient. At this time in medicine, no one is to be sure. However, we do not know if it is beneficial, the FDA will have made wise decision. Alternatively, if DDI has no benefit, the decision will be a catastrophe. The concerns about only approving therapies proven to be safe and efficacious may have been partially replaced by pressure and political considerations.

Dr. Scher points out that the payment to physicians on a per capita basis may also introduce additional problems; i.e., physicians may enter patients into a trial who may not meet eligibility requirements. There are many restrictions of the trial, including the prospect of selective quality control and the possibility that the per capita payment, rather than the success of the trial, may be the goal.

Professor Royall notes that the consent process is critical in light of the five problems discussed in my paper. I believe it is also critical in the fifth problem where the FDA requires at least two well-constructed trials. It is difficult to envision a patient agreeing to enter a confirmatory trial when told that a beneficial treatment exists.

I am in disagreement with Professor Royall's remarks that when a patient drops out of a double-blinded study, he/she should not have access to the treatment received, provided the consent document discussed this aspect fully. Dr. Ellenberg also holds this position. My view is that a patient consent bargain rights away and is informed about the blinding in a consent document is immaterial. Furthermore, it is difficult to envision how the release of such information can prejudice a patient's decision.

Dr. Freedman's comments raise many interesting points. He (and Dr. Ellenberg) quite rightly point out that "money is not the sole, nor necessarily the most prominent inducement" for a physician to join a study. Although he agrees with my general concern that there may be pressure upon physicians to enter patients on trial, he attributes my main concern to a possible excess reimbursement. Although excess reimbursement may occur, this is not my prime concern. My concern is that the physician should "pass over backwards" in revealing the patient any transfer of funds for patient participations. In the event a patient discovers that funds have been transferred, it can only damage the physician-patient relationship. In fact there are many clinical trials where the compensation does not cover the increased costs of a patient being on a clinical trial. Nevertheless, the issue concerning the patient whether the physician's judgement has been influenced by the reimbursement. Furthermore, the deception may make the physician "guilty of assent" in the eyes of the patient.

Dr. Ellenberg states that "the practice of per patient reimbursement to physicians for clinical trial accrual has been extensively discussed." I am not familiar with the body of literature that is cited. The literature I am familiar with deals with the ethical concerns of patient (not physician) reimbursement. As noted earlier, Dr. Ellenberg remarks that there are other financial inducements for a physician to enter patients on trials. However, our society is especially sensitive to financial transactions and views with suspicion attempts to keep such transactions secret. The inclusion of pharmaceutical recognition is not accorded the same status for suspicion as money.

She has raised concerns about the widespread practice of judging outcomes in a clinical trial using a 5% significance level. She challenges the widespread use of the significance level as a long-standing criterion of the current practice of utilizing tests of significance without considerations of the general consequences of courses of action. If there is a large number of momentous waiting to be evaluated, the trials should be designed differently compared to a situation where there are few or no momentous waiting to be evaluated. The idea is to design the trials to find beneficial treatments as early as possible.

Dr. Ellenberg states the issue of whether my position on confirmatory trials has changed. In earlier publications, cited by Dr. Ellenberg, I have shown that the probability of a positive finding by any one observer from a clinical trial may be disappointingly low. One way to increase positive results is to have independent confirmatory trials. This is obviously the reason why the FDA has required at least two independent trials. However, I have changed this point of view for trials evaluating therapies for the treatment of life-threatening disease. Unless, of course, there are serious questions about the conclusions of the first study. The reason for this change is that it is unethical to carry out a confirmatory trial unless it is an equivalence trial. In some instances it might be a better strategy to place a larger study at the outset, then an initial study which may be followed by a confirmatory trial. For example, if, we cannot having a 0.05 level of significance with a power of 0.95, require more patients than a single trial having a 0.05 significance level and a power of 0.99. However, the recent decision by the FDA to approve drugs without any complete trials at all, may make the entire process more attractive. In such instances, it would be mandatory to have post-marketing surveillance for all approved drugs lacking definitive scientific evidence.

Reference

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