Biopharmaceutical Section

American Statistical Association

Biopharmaceutical Report

Volume 1, No. 1 Winter 1992

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 patient; (ii) the conflicts in choosing a patient population (newly diagnosed or refractory to known beneficial treatments) 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 Byar et al. (1990), Royall and the discussion (1991), Hellman and Hellman (1991) and Passamani (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 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 Gilks and Ware (1990) discusses the situation in Kenya and raises the issue, should such research be

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stopped until the counselors are in place. Their letter was in response to an editorial in the *New England Journal of Medicine* by Angell (1988) that addressed the issue of "ethical imperialism." Gilks and Ware interpret ethical imperialism as "the imposition on one society of solutions culturally appropriate to another society, on the pretext that they represent cultural absolutes." Debates on the moral justification for a course of action must be particularly sensitive to these concerns. The debate on ethical imperialism has been motivated by the potential for Western countries to carry out studies in Developing countries that would not have been allowed in the West due to ethical considerations. The debate has been unidirectional where the ethics of the West are to be imposed on developing countries. In essence the tacit agreement appears to be that the sponsors of the research have the authority to demand that their ethics be imposed. A two-way debate would consider whether the ethics of human investigations in Developing countries should also be adhered to in the West when there is a joint collaboration.

The Nuremberg Code was issued in 1947 during the Nuremberg War Crime Trials. It set forth the standards on how to judge the Nazi physicians and scientists who conducted brutal experiments on concentration camp prisoners. The Nuremberg 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 unifying 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 to the Commission; e.g. "to identify 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 reflects 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" incorporates at least two ethical convictions: (i) individuals should be treated as autonomous agents and (ii) persons with diminished autonomy are entitled to protection. "Beneficence" in the Belmont Report is interpreted to maximize possible benefits and minimize possible harm. It makes the interesting observation that avoiding harm requires learning what is harmful. In the process of obtaining this information, persons may be exposed to the risk of harm. "Justice" is interpreted as "fairness in distribution." 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 (if he/she is in private practice) or the physician's hospital receives 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" trials and reimburses grantee institutions additional per capita funds for each patient entered on such trials. Ostensibly, the funds are awarded in order to cover the extra costs incurred by the physicians in collecting additional data required by the trial. In some instances the funding may be an incentive to help persuade the physician to enter a patient on a clinical trial. It is rare to set the payment according to a cost accounting study of the necessary additional costs incurred. Actually, in many industry-supported studies, the data are usually collected by study monitors, employed by industry, who visit physician offices and abstract relevant data from the patient record. If a physician is in private

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 Report*. There are two main purposes for the *Report:*

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

b) To provide a vehicle for scientific interchange through invited articles, reviews, and discussions, as well as short contributed 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 contributed non-technical papers, points of view, and reviews of software and books. Any suggestions of improvement of the *Report* are also welcome.

I would like to thank several people who helped me put together this first issue. First of all, I would like to thank Professor Zelen for his excellent paper, and all the discussants for their insightful comments and their timeliness. I would also like to thank Camilla Brooks for analyzing the results of the Best Presentation in ASA 1991 and the other people who contributed to this issue. Additional thanks go to Bob Davis and Louise Ryan who have helped me consistently in editing, and to Nina Mocniak for designing the logo. Finally, I would like to thank Gladys Reynolds 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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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 in which there is a problem accruing patients. The payment of such funds is generally unknown to the patient contemplating going on a trial. If the consenting 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 patient be informed about the payment to the physician or 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 patient 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 have some beneficial value. An ethical 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 patient 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. There does not seem to be a clear cut answer to this problem. The final decision on choice of population may depend on other factors associated with the beneficial therapy; e.g. cost, side effects, long-term benefit, success 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; reports discussing the use of streptokinase for the treatment of infarcts. The first two examples prompted 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 non-dramatic results of the trial (or even 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 patient be notified with 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

Sessions 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 talks will be given by Ron Kershner from Sterling Drug, Inc., and Robert O'Neill from the FDA. The two discussants will be Thomas Fleming from the University of Washington and Laurence Freedman from the NCI.

Dietary Quantification—Estimating a Moving Target

Chair/Organizer: Mikel Aickin, University of Arizona.

There will be three talks in this session. They will be given by Laurence Freedman from the NCI, Valerie Tarasuk from the Ontario Worker's Compensation Institute and Lisa McShane from the National Institute for Neurological Diseases and Stroke.

Estimation after Sequential Stopping

Organizer: Scott Emerson, University of Arizona.
Session Chair: Philip Banks, University of Arizona

Three talks will be given by Kyungmann Kim from Harvard University, Karen Facey and John Whitehead from the University of Reading, and Scott Emerson and Philip Banks from the University of Arizona. Bruce Turnbull will be the discussant.

Statistical Problems in Estimating HIV Seroprevalence

Chair/Organizer: John Karon, Centers for Disease Control

Three talks will be given by Nicholas Jewell from the University of California at Berkeley, Donald Hoover from Johns Hopkins University (with Alvaro Munoz and Vincent Carey) and Glen Satten from the Centers for Disease Control. The discussant will be Meade Morgan from the Centers for Disease Control.

Best Presentation of a Contributed Paper, ASA 1991

In order to encourage better presentations by Section members at the Joint Annual Meetings of the ASA, the Biopharmaceutical Section initiated an awards program for contributed papers in Section sponsored sessions. The audience in all the Sessions received evaluation forms and were asked to evaluate the presentations on organization, verbal delivery, visuals, handouts, and overall. Session chairs were a great help in reminding the audience several times throughout the Sessions to fill out the evaluations. A total of 307 forms were collected at the six contributed Sessions. Thirty-seven presentations were evaluated, with the number of evaluations on a paper ranging from 11 to 70. The rating scale on each item was from 1.0 to 4.0. The mean scores ranged from 1.9 to 3.3, with a median of 2.7. There were three papers with identical mean scores of 3.3.

The three winning papers are:

1. "Pharmacodynamics of Analgesia Produced by Morphine and One of its Metabolites," by Thaler, H.T., Friedlander-Klar, H., Portenoy, R.D., Inturris, C., and Foley, K., from Memorial Sloane-Kettering Cancer Center;

2. "A New Statistical Method for Analyzing the CHO/HGPRT Mutation Assay," by Roth, A.J., from G. D. Searle & Co.;

3. "Ratio Estimates, the Delta Method, and Quantal Response Tests for Increased Carcinogenicity," Bieler, G.S. and Williams, R.L. from Research Triangle Institute.

The Section would like to congratulate the three presenters for their excellent presentations and to encourage all members to continue to deliver well organized, high quality papers. The winners will receive a plaque acknowledging this award and a cash award of $250 at the 1992 meetings in Boston.

The Awards Committee of the Section is now assessing how well the process itself worked, since this is the first experience the Section has in awards. Some enhancements were already suggested for the next meeting. If you have any suggestions to the Awards Committee, or would like to volunteer to help in the awards administration, please contact Camilla Brooks, Avital Cnaan, Lilliam Kingsbury, or John Schultz.

announcement. Furthermore, advice should be given on current and future treatment program. This is especially important for patients who have or are receiving an inferior therapy.

Double Blind Trials

Some trials are conducted as double blind trials where both the patient and the attending physician are unaware of the actual treatment. Of course the patient has been notified in the consent process 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 agrees that the patient should not be informed until after the research is concluded, if informing 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's request for breaking the blinding be honored? Since the patient is no longer officially on the trial it would appear that full disclosure should be made to the patient by the responsible physician. A case 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 patient's future prognosis may be dependent on revealing the blinded treatment.

Food and Drug Administration (FDA) and Confirmatory Trials

The FDA issues guidelines to assist applicants 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 (plural) has been interpreted to mean that the effectiveness of a drug should be supported by more than well-controlled trial. ...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 investigation ...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 unrepeatable on ethical grounds. ...Such cases are unusual and an applicant seeking to invoke these exceptional circumstances must provide strong support for this position" (FDA, 1986, pp 19-20).

The requirements for more than 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 setting should be regarded as being very different than a laboratory setting where independent replication of a finding does not raise 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 "equivalency trial" where the 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 an "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 at approximately the same time. Sometimes, the confirmatory trials are made on a different patient population or at a different dose level. Nevertheless the entire process does not seem defensible. It would be an "awkward" problem for the physician to notify the patient that the trial is a confirmatory one where an earlier trial showed the superiority of the drug. It is of some concern how the patient consent process is carried out when the physician is obliged to tell the patient 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 bears the marks of omniscience. Several examples 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 therapies to treat AIDS, is piloting a trial on pregnant women who are HIV positive. It is estimated the 15-30%

of the infants will eventually be diagnosed as seropositive 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 (OPRR), NIH, 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 OPRR 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 OPRR decision has overridden 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 unethical research regardless of their scientific merit ... The approval of the institutional 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 vetoes decisions reached by local review boards is in the precarious position of claiming to have insight into ethical matters that is superior to that of all others and so to be justified is unilaterally rejecting decisions made by duly constituted review boards. The validity of such claims is dubious, indeed, although examples of such judgmental arrogance are hardly absent. A veto also raises the interesting question of why review boards should be established in the first place if their decisions can be easily rejected by someone far removed from the scene who claims ethical omniscience."

The OPRR and editors of journals are in a certain sense omnipotent. They should be sensitive 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 witticism. "How does the (government, editor, etc.) make decisions? The same way a gorilla makes love! How does a gorilla make love?—Any way it wants to!"

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Midwest Biopharmaceutical Statistics Workshop Muncie, Indiana May 22 to May 24, 1991

As we are approaching the Midwest Biopharmaceutical Statistics Workshop for 1992, here is a quick reminder of some highlights from 1991.

ASA President Arnold Zellner spoke about the growth of the ASA and the need for statistics in every facet of science and industry. One interesting session dealt with population pharmacokinetics. Wayne Colburn, from Harris Labs, did not support NONMEM, asking for validation of it, including an evaluation of robustness to error structures which do not have a normal distribution. Several people emphasized the importance of good experimental design procedures. In yet another session, concerning Phase I clinical trials, Douglas Faries presented an adaptive sequential method for estimation of the MTD. James Bolognese presented an alternating panel design. Carl Metzler suggested a sequential crossover design in order to use fewer subjects at lower, presumably less effective doses.

Discussion

Robert M. Veatch

Georgetown University

Dr. Zelen has once again raised for us some interesting and important questions about the ethics of clinical trials. What seems to be missing, however, is any sense of a core ethical vantage point from which one might approach his questions. I suspect that only with some such perspective providing a foundation for ethical

reflection will there be a chance of dealing with the questions he raises (Levine, 1987).

A hint 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 relativism (the view that different cultures at different times appear to hold different moral positions). He uses this to support the claim that "there is no single absolute standard for ethical behavior." But from the fact that cultures differ on ethical judgments, it does not follow that there is no single absolute standard for ethics any more than it follows from the fact that different cultures at different times have had different accounts 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, "Provide counseling whenever 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 consistent 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 reasonably informed decision makes, will the answers to these questions emerge.

Rational people would agree to be in a clinical trial only when they are relatively indifferent to the treatment options. They are at or near what I have called the "indifference point."[1] At that point the null 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. (The patient will not care which arm her 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 bounty trials the key question is, "Would a reasonable patient want to know the fact that his physician is being paid a bounty to recruit him into a trial?" It seems obvious that many such patients would want to know. Dr. Zelen is surely right here. They might even justly claim a portion of the payout.

Likewise, the perspective of the subject as active moral participant provides a basis for deciding which population should be part of Phase II clinical trials. Only those patients who are relatively indifferent between the treatment arms would reasonably agree to be randomized. These may be patients who have done poorly with other therapies (but fear the risks of the new therapy) or it may be those who have not yet tried more conventional treatment, but particularly disvalue its risks while at the same time feeling particularly attracted to the possible benefits of the new therapy. For ethical purposes, some of each group may be acceptable; others in either group may not be.

So also this framework provides a basis for dealing with the question of communicating findings. If patients have a moral right to be told what they would reasonably want to know, then the only question is whether patients would like to know the findings. I can't imagine they would not. In fact, this creates a more serious ethical problem than Zelen mentions. Even as a trial progresses, if there is a sequential design with preliminary data analysis as the study progresses, we need to ask whether patients would rationally want to know the preliminary findings. A subject who was more or less indifferent at the beginning of a trial might rationally prefer one treatment arm or the other as preliminary data become available even though it is scientifically and morally necessary to continue the trial until more reliable data are produced (Veatch, 1979). It is rational to make use of weak or preliminary data when a decisions must be made and nothing better is available. Likewise, subjects would rationally be influenced by the data from pilot studies and earlier trials even though the conclusions are not firm enough to cease replications. Patients who begin at or near the indifference point who need treatment immediately would reasonably use such data to determine whether they remain indifferent to the options.

Subjects who understand would also insist on the right to know when they leave a trial the arm of the study they are in. Such information could be crucial. If patients are truly active participants in the trial, they would impose this as a condition of their willingness to be in the trial.

Finally, the concept of a subjective indifference point and subjects who are active moral agents provides a solution to the problem of confirmatory trials. Different people will be indifferent to two treatment options at different times. An initial trial is morally acceptable when a significant number of people (and investigators) honestly do not know which of two benefit/risk packages is better. After an initial study many of those people should no longer be completely indifferent. But just as data emerge that sway them in one direction, a new group of people (those originally preferring the now less favored arm) move into the zone of indifference. It would be immoral to pressure the no longer indifferent patients into a randomized confirmatory study, but there is nothing morally wrong with asking the newly indifferent group to volunteer to be randomized. If there is lingering doubt about the attractiveness of the winning arm in the initial study, then some subjects who are now more or less indifferent should be available to volunteer for randomization.

At this point morality calls not for pre-randomization (Zelen, 1981), but a semi-randomization in which those who prefer one arm (standard or experimental) receive it while those who are relatively indifferent are randomized (Veatch, 1983). If there are those who are indifferent, there is nothing wrong with doing a confirmatory study with them. If no one is relatively indifferent, then the null hypotheses is no longer plausible and further study would be immoral.

It seems to me the key to all the questions raised by Dr. Zelen is whether we are willing to follow the principle of respect for persons to its implications for informing them, giving them the option to participate actively in the design and conduct of the trial, and giving them information about its outcome. If this perspective is taken, I believe answers to Dr. Zelen's questions can be found.

[1]Patients are at the indifference point when they are more or less indifferent between two or more treatment options considering all the potential risks and benefits as they evaluate them subjectively. If patients have a modest preference for one arm, that is if they are near but not at the indifference point, it is not unethical to ask them to be modestly altruistic and take a chance of getting the arm less desirable to them. Hence it is wrong to say that the best interest of the subject must always come first, but rational people would not deviate too greatly from their interests. On the subject of why it is rational for patients to have subjective preferences for one arm or another even if data are not available see Veatch, Robert M. (1979).

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Discussion

Stanley S. Schor

Merck & 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 five issues raised by Dr. Zelen and then raise one of my own. Since I am limited in space I will mention only the more 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 admitting 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 one step 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 unwarranted risks? Most clinical trials are performed on people who have only the disease to be treated and no other.

Yet most people with that disease have other debilitating 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 scientific papers appear. They volunteered for the study and the least that can be done 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 requirement 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'ers require the same end points 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 two out of three positive, or two studies at 90% power to have an 80% chance of having them both be positive? In both cases more patients must be experimented 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 Merck 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 that viewing those in the light of informed consent goes a long way towards clarifying them.

The consent requirement implies that the subjects in a clinical trial must be fully informed about any 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 relevant that 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.

Biopharmaceutical Work Groups, ASA 1991

Organized and summarized by Nick Teoh

The Biopharmaceutical Section had several well-attended roundtable luncheons during the 1991 Joint Statistical Meetings. In addition to having a good lunch, most attendees were also able to interact with the discussion leaders and glean 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, attendees also had the opportunity to make enquiries and, if interested, formally join the work group as a participating member. Alternatively, attendees could also solicit interested participants to form a new work group. Such indeed was the case with a new work group lead by Christy Chuang- Stein that will be focusing on dose-ranging study designs. This new group is currently comprised of eight attendees (from seven different companies) of the luncheon. However, anyone else who is interested in similar kinds of joint work is still welcome to join this and/or other work groups irrespective of their attendance at the luncheons. Interested members of the biopharmaceutical section who would like to obtain additional information on the various work groups or who wish to organize new work groups may contact Nick Teoh at Abbot Laboratories, Dept. D-436/AP9A, Abbott Park, IL 60064 [Tel.: (708) 737-4451)].

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

Dose-Ranging Studies: Parallel Design vs. Titration Design

Christy Chuang-Stein

This was a well-attended luncheon with participants from seven different pharmaceutical companies. The participants shared various aspects of their own experiences in the design of dose- ranging trials as well as ideas on the ideal strategy to adopt for such trials. The discussion ended on an enthusiastic note with a unanimous request by the participants that a new biopharmaceutical work group be organized to do further research on this subject. The proposed charter of the work group will be to focus on identifying the roles 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 plans for this work group has been circulated to the participants for additional input. Interested members of this section who are prepared to "roll up their sleeves and do some research work" on this topic should contact Christy Chuang-Stein at The Upjohn Company [Tel.: (616) 385- 7872].

More synopses can be found on the following pages

Informed consent to participate in a clinical trial represents much more; it is in fact an agreement in which the patient accepts specific changes in the usual way that treatment is selected and applied. If the trial is randomized, the patient agrees to allow his treatment to be selected, not by the usual criteria (in which the first consideration is which treatment is best for him, in his and his physician's judgement), but by chance. He might also agree, for example, that a protocol will be followed that allows for less flexibility in adjusting the treatment to his specific conditions than would be the case if he were not in the trial. By entering into this agreement he receives certain benefits also. For example, he might get a fifty-fifty chance at receiving a promising new drug that is unavailable outside the trial. Or he might receive no other benefit than the satisfaction of participating in what he judges to be a worthwhile endeavor.

The consent requirement in clinical research replaces the most difficult ethical issues (such as whether the physician can be justified in giving his patient drug A when he believes drug B will be better), with easier ones (whether the physician can be justified in asking the same patient if he wants to participate in a clinical trial where the treatment, A or B, will be selected by chance). It also raises practical problems of education and communication (how to present the information so that the patient understands enough to make a free and informed choice). In Professor Zelen's second problem, choice of a patient population for Phase II trials, the consent requirement shifts the question from "which population should we use?" to "Will enough patients in the population that we want to use, when made fully aware of the study, its risks and uncertainties, its goals and potential value, choose to participate?" The next two issues discussed by Professor Zelen concern the sharing of information with patients and their attending physicians. Clearly information should be shared as early as possible about any aspect of the study that might be relevant to therapeutic decisions. The only justifiable departures from this policy are ones that are essential for the success of the study (such as the "blinding" of treatments) and about which agreement was reached in the informed consent process. If telling a patient who drops out of a blinded study which treatment he was on will jeopardize the study, then this should be spelled out in the consent agreement, where it should be explained that although he is free to drop out of the study at any time, he might not have access to treatment information until some endpoint has been reached.

Only in Professor Zelen's fifth example, FDA policy regarding confirmatory trials, does informed consent seem to be a tangential issue. When does the FDA have enough evidence for the safety and efficacy of a drug to grant approval? To answer the question requires weighing the costs of further trials against the risk associated with immediate approval. As Professor Zelen suggests, the latter risks might by reduced by careful postmarketing surveillance.

The costs of further trials are of two types, the direct costs of doing further studies, and the less tangible costs of withholding the new drug from patients it might help. If the new drug is available only to those who participate in a confirmatory trial, the physician convinced of its superior efficacy will be frustrated by his inability to prescribe it at will, but he faces no ethical dilemma—he is doing his best for his patient by encouraging him to participate in the trial. (Lockwood, 1983, gives a good analysis of the ethics of similar situations.)

I believe that FDA insistence on confirmatory trials can be justified in individual cases, but not as a general policy. The requirement is appropriate when it is based on a conscientious evaluation and judgement that for this drug, considering its potential value and risks in relation to available alternatives, a confirmatory trial is needed. It is unethical when based on bureaucratic conservatism.

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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 in the Informed Consent regarding so-called "bounties" for patients entered into clinical trials. Dr. Zelen's reasoning is fine, 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 a non-investigator physician has 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 non-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 surrogate endpoints without altering the patient's quality of life or survival. This is true of a large number of therapies employed in all areas of medicine and especially cancer medicine. Unlike other areas of science, medicine does not frequently declare a therapy "ineffective" 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 treatment of choice for most patients until an equally radical but somewhat more palatable treatment could be substituted: lumpectomy plus radiotherapy. This therapy also has very little impact on patient survival, and it is debatable whether all patients' lives are improved by having lumpectomy followed by immediate radiotherapy rather than lumpectomy 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 benefitted 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 palliating symptoms or improving 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 tumor regression, 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 he/she has relatively few symptoms but feels uncomfortable doing nothing, or late in the patient's course when suffering is maximal and all active treatments have been tried?

1991 Biopharmaceutical Work Groups (continued)

Randomized Concentration-Controlled Trials (RCCT)

Lianng Yuh

The focus of the discussion, which was led by Lianng Yuh and Lilly Sanathanan, was centered on utilizing pharmacokinetic data to choose an optimal dose or drug concentration. Instead of randomizing patients into different dose levels, Peck and Rodman (1991), and Sanathanan and Peck (in press) had suggested that patients should be randomized into different pre-determined 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, RCCT's are more efficient than conventional dose-ranging designs if there is a significant pharmacokinetic-pharmacodynamic correlation. Some of the topics that were discussed among this group of outspoken luncheon participants included:

- The role of the placebo treatment group in RCCT'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 covariate.
- Advantages and disadvantages of RCCT's.
- Alternative models (e.g., measurement error models).
- Comparison of RCCT's with other designs.

In addition, the role of RCCT's in Phase I-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 RCCT's could be particularly useful for studying drugs with narrow therapeutic windows.

Population Pharmacokinetic Modeling Work Group

Ken Kowalski/Lianng Yuh

Members of this work group met during the Joint Meetings at Atlanta to plan their goals for 1991-1992. One of the immediate goals of the group is to assemble an extensive bibliography of references connected 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. Interested members of this section who wish to participate in the research activities of this work group may contact Lianng Yuh at Parke-Davis [Tel.: (313) 996-7854].

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 at this luncheon taught courses for engineers and medical research personnel. Their current course philosophies and contents included statistical reasoning, statistical concepts, statistical methods, 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 clients' subject matter area.
- Learn the clients' subject matter and local terminology before designing/teaching a course.
- Connect statistical concepts and methods to user-friendly software.

Don't

- Teach theory; but if unavoidable, relate 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 luncheon discussion was presentations for grades K-12 by biopharmaceutical statisticians. In addition, some of the avenues for teaching statistics that are available through the ASA and the Qualitative Literacy (QL) program were also discussed. Some of the many creative ideas shared involved performing a randomized clinical trial in the classroom and analyzing the outcomes; designing an exercise to illustrate the project team concept and the data flow concept; asking children what they want to be when they grow up, and then discussing how statistics is used in that field; and varying popping times in making popcorn and seeing how that affects the number of unpopped popcorn kernels. The participants proposed various tips and strategies including: don't try to do too much; hold the students' attention and keep things moving; have them participate; have two or three adults assist; and most of all—have fun!

Participants of this luncheon agreed that brief 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 problem sets that kindergartners through adults can relate to. The participants also expressed the hope that companies with summer internship programs will consider using teachers as interns.

I fully concur with Dr. Zelen's comments regarding the communication of findings from clinical trials, but I would go a little further than he has. Shouldn't all patients 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 physician/investigators, we frequently argue that a therapy will no longer be 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 detected by the elevation 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 requirement for confirmatory trials does not seem to address the issue of false positive results. Dr. Zelen once wrote a paper suggesting that approximately half of all published trial results represent false positives, and I believe that we could easily find many instances in the history of medicine where such false positives have resulted in misery for thousands or even millions of patients over decades or centuries. Possibly the example of the radical mastectomy applies here, as well. To me the solution to the problem is not to lower the standards by approving drugs on the basis of a single trial, but rather to insist 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 high-dose chemotherapy and autologous bone marrow transplant is a good example of the inappropriate use and acceptance of prolonged Phase II trails (as well as the inappropriate publication of premature results without information of the important endpoint of such studies—survival).

Discussion[1]

Benjamin Freedman

McGill University

Not long ago, the only financial issues dealt with by those writing on the ethics of clinical trials concerned payment to subjects: When should it be permitted? When is it excessive (Macklin, 1981; Ackerman, 1989)? 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]The author gratefully acknowledges support provided in preparing this article by grant #806-91-0031, awarded from the Social Sciences and Humanities Research Council of Canada's program in applied ethics..

paying investigators for participation in research has been sparse. Professor Zelen is to be commended for courage and pertinence in raising the issue of reimbursement mechanisms for investigators. But the questions raised are numerous, and highlight important and subtle ethical choices. 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 there are questions other than consent worth asking. The ethics of clinical 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 unduly distort the balance at any one of these stages, for example, by leading an investigator to squander his or her own scarce resource, 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. As a first step in examination of this issue, we may distinguish between issues arising from the source of payments, the form in which payments are calculated and made, and the destination of payments.

Sources

University researchers and members of research ethics committees (IRBs) are inclined to look most closely and skeptically at studies funded by drug companies. As Dr. Zelen points out, however, similarly troubling financial arrangements—e.g., "bounty" 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 joining a study as an investigator and recruiting subjects. If we are justified in examining the propriety of inducements for investigator participation, and considering such reforms as disclosing them to subjects in an informed consent document, we must proceed upon the basis of a broad, accurate and fair inventory of investigator inducements. Simply listing oneself 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.

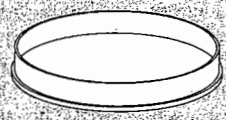
It is not good enough to focus upon payment, and to fail to consider other forms of professional inducement purely on the grounds that payment is quantifiable. Those other factors can be quantified as well; indeed, they commonly are, in institutional policies on promotion and tenure.

Are there other troubling sources of payment? If the only source of concern in investigators' payments were that of deception of research subjects, it would follow that studies that are paid for by subjects themselves (as in some institutional arrangements for investigative cancer treatments, e.g., biological modifiers) would not be an object of concern. If, to the contrary, any arrangements that distort the ethical balance of the planning and conduct of trials is worrisome, patient-funded research surely qualifies. One bottom line question for these arrangements is: Will payment distort the researcher's scientific or clinical judgment, in his or her plan for intervening in ways that will further medical science while not compromising the patient's medical chances? In examining the source 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 foreclose that possibility.

FDA CORNER

We would like to establish a corner to give FDA perspectives, thoughts, interesting issues at advisory committees, etc. In order to open this corner, we begin with a poem written by Dr. ***Tie-Hua Ng****, ex-FDAer (author's terminology).*

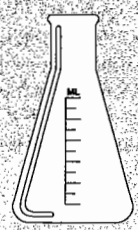
My Life at FDA



Type I error is what I care,
Active control is what I scare,
Sample size is what I need,
Equivalence is hard to get.

Interim looks have to pay a price,
Unbiasedness requires double-blind,
Placebo-control is what I love,
Bad studies are hard to serve.

Multiple endpoints need adjustment,
Stopping rules must be properly set,
Multicenter produces interaction,
Good studies require careful randomization.



Efficacy is not all I care,
Safety may be what I scare,
Confidence is what I need,
Power may be hard to get.

Forms of Payment

What is most troubling about arrangements for paying investigators? Is it the amount that is paid? The manner 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 seems more disturbed by the excess 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 to the detriment of researchers, rather than to their advantage, leading to a net cost rather than profit per patient (Lewis, 1988). My own (limited) experience in reviewing

financial arrangements of trials (especially those under drug company sponsorship) suggests Dr. Zelen's is the more credible claim, but I will leave that question for the reader to judge. Both positions at any rate underestimate the impact that the simple amount of funding can have upon the priorities of a researcher or research unit. Given, again, Dr. Zelen's concern about disclosure, it might indeed make sense to inform patients (that is, prospective subjects) about the profit that their enrollment represents, while making no sense to tell patients about the magnitude of the study, or the proportion of team effort its conduct represents. Given my broader concerns about mixed motives and agendas, though, the simple fact of size is indeed important: Big money speaks loudly.

The facet of researcher payment that most disturbs Dr. Zelen is neither size nor excess value, but rather the way to calculate reimbursement, namely, the provision of capitated payments. If a researcher gets a set sum of money for each patient enrolled, Dr. Zelen feels, this fact must be disclosed to prospective subjects.

The concern with per capita payments does not stand alone. If, for example, a capitated payment exactly covered the incremental cost of enrolling a given subject, it does not appear that Dr. Zelen would be so uneasy; and indeed, payment by capitation rather than project participation has been defended on the grounds that it is the most precise basis for reimbursement (Lewis, 1988). But costs are not precisely calculated, resulting in a discrete financial inducement to enroll a subject that recurs with each referral.

I therefore share some of Dr. Zelen's concern with capitation, while still insisting the problem is not sui generis. Is there any way to assuage this concern? One suggestion: Per-capita payments to investigators should at least be pro-rated, so that a subject who has completed half of a study should ground half of the investigator's payment. The research committee on which I serve, in common with many others, has insisted upon pro-rated payments to subjects, so that they are not coerced into incautiously completing a study into which they have a sunk investment of time and discomfort. The same considerations apply to researchers, who should not be structurally induced to retain a subject upon protocol past the point of safety or clinical prudence.

Destination

A third question to be asked about payment is *Cui bono*?— who benefits from payment, and how? Again, I believe a functional ethical analysis is required rather than action upon intuition; two examples, drawn from the same source, will illustrate this.

An anonymous journal inquiry concerned the payment of finder's fees to medical residents who refer patients as prospective research subjects (Anonymous, 1990). This practice was described as 'troubling'. Indeed, we may infer that finder's fees bother the author even more than the payment of an investigator's fee itself from the fact that an element of proposed policy described by the author requires that the 'finder' be actively involved in the protocol (thus, transforming the transaction from a finder's fee into investigator's payment). On examination, though, it seems clear that payment for finding subjects is much less ethically worrisome than payment for recruiting them and holding on to them. The likelihood that a patient's interests will be compromised by the recruiter is much less than is the case for the investigator.

The other preliminary rectification suggested in that anonymous note was that the finder's fee come as a bookstore voucher rather than cash. Again, the solution appeals to instincts more than to reason. One may reasonably feel that a bookstore voucher is no less valuable than its cash equivalent, in which case the restriction makes no sense. If it is less valuable, though, given my argument that there is less that is ethically problematic in finding than recruiting subjects, why should the former be less reimbursable?

The points can be generalized. Rather than asking who gets paid for research participation—investigator, clinical fellow, nurse, technician—we need to wonder how this will affect conduct towards subjects. And rather than privileging some forms of payment—e.g., that which will be directed towards a discretionary research fund in the department, rather than to the pockets of investigators—we need to similarly ask what functional difference payment will make to the beliefs and conduct of those in whom a patient's fate is entrusted.

In conclusion: The problem of investigator's payment reveals upon further analysis the involvement of interlocking puzzles: What is 'payment,' and are other professional inducements problematic? Are some funding sources, or funding arrangements, intrinsically less likely to generate ethical conflict than others? These are issues that research ethics committees need to examine, soberly and realistically. 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 conversation.

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Discussion

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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 considered ethical by individuals and/or groups will vary, both with geography and with time. As Dr. Zelen notes, this variation may lead to difficult problems in conducting multinational trials; and 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 I do agree that most of the issues he raises present ethical issues that are worth discussing. The practice of per-patient 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. There must, of course, be some provision for payment of research costs—and there needs to be some incentive system if we believe that clinical trials, particularly of potential life- extending therapies, should be carried out in the most rapid and efficient way possible. Trial sponsors, especially the federal government, would be properly criticized if its provision of research funds to clinical investigators was entirely independent of these investigators' ability and willingness to enter patients on trials. One might argue that a sponsor who 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 arranging 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 routinely enter large numbers of patients are likely to become chairpersons of trials and attain a higher level of visibility in their profession. Should such arrangements, or likely consequences, also be revealed on consent 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 testicular 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 most 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 tendency for patients themselves to demand access to new therapies, whether or not a beneficial therapy is available. Despite the fact that AZT has been clearly demonstrated to prolong life, 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 regard to 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 designed in such a way as 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 potential 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's need to know outweighs 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 exercised with some flexibility. This issue is part and parcel of the overall concerns raised over the decades of the ethics of randomized trials in general. How long should an individual trial continue? Should we stop a trial before the planned accrual and follow-up is complete if the results appear definitive? There are some who would say that as soon as any trend emerges, it becomes unethical to continue randomization. It appears to me that the generally accepted requirement for demonstration of efficacy—that study results be inconsistent with the null hypothesis of no treatment effect at the .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 (Peto, 1987). There is clearly a continuum of magnitude of information, and the FDA policy may be on the conservative end; but Dr.Zelen and others have provided a rationale for such conservatism in many circumstances (Zelen, et al.,1980; Staquet, 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 can 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 probability decreases to 64%, and a 1% rate implies that a drug found effective in a clinical trial has only a 14% chance of being truly effective. (These calculations are based on the assumption of 80% 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 publicize it, have as 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 a wide consensus about new and difficult ethical issues, a process requiring the types of public airing of different perspectives that Dr. Zelen cites.

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Rejoinder

Marvin Zelen

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I wish to thank all of the discussants for their commentary on my paper. They all agree that the problems raised require more serious attention. In addition, several have amplified related 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 reverse alphabetical order of the discussants.

Professor Veatch has authored a scholarly book (Veatch, 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 principal 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 desirable 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 bizarre and controversial this Hippocratic ethic is and how strange it would be if modern, rational people, whether operating out of the religious or secular moral framework, were to revive the ethic of the Pythagorean–Hippocratic cult."

Professor Veatch remarks that rational people would agree to participate in a clinical trial when they are indifferent to treatment options. There is no dispute about this axiom. However, its implication 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 patient, and, in many instances, the physician, is under duress which may interfere with free communication. These same issues arise in participation of Phase II and confirmatory trials.

Dr. Schor 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 formally gave drug approval even though no clinical trials were completed showing that DDI prolonged survival. Approval was based on laboratory data showing that DDI raised the CD4 counts of DDI-treated AIDS patients. The clinical trials evaluating AIDS are yet to be completed.

Thus it appears 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 of the benefit and safety of such approved drugs be mandatory. At this moment in time, no one knows if DDI is beneficial. Eventually we will know. If it is beneficial, the FDA will have made a good 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 politics.

Dr. Schor 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 ramifications of this issue, including the prospect of selective quality control and the possibility that the per capita payment, rather than the science of the trial, may be the goal.

Professor Royall writes that the consent process is critical in four 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-controlled 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-blind 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 cannot bargain rights away and being informed about the blinding in a consent document is immaterial. Furthermore, it is difficult to envision how the release of such information can jeopardize a study.

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 about informing the patient about physician payment for entering 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 "lean over backwards" in revealing to the patient any transfer of funds for patient participation. In the event that a patient discovers later 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 is whether the physician's judgement has been influenced by the reimbursement. Furthermore, the deception may make the physician "guilty of something" in the eyes of the patient.

Dr. Ellenberg states that "the practice of per-patient reimbursement to physicians for clinical trials accrual has been extensively discussed." I am not familiar with the body of literature she is citing. 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 non- 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 inducement of professional recognition is not accorded the same status for suspicion as money.

She has raised concern about the widespread practice of judging outcomes in a clinical trial using a 5% significance level. She certainly is correct. Actually, this is a long-standing criticism 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 treatments waiting to be evaluated, the trials should be designed differently compared to a situation where there are few or no therapies waiting to be evaluated. The idea is to design the trials to find beneficial therapies as early as possible.

Dr. Ellenberg raises 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 being a true positive from a clinical trial may be disappointingly low. One way to improve the true positive rate is to have independent confirmatory trials. This is undoubtedly 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 diseases. (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 plan a larger study at the outset, than an initial study which may be followed by a confirmatory trial. For example, two trials, each having a .05 level of significance with a power of .95, require more patients than a single trial having a .01 significance level and a power of 0.99. However, the recent decision by the FDA to approve drugs without any completed trials at all, may make this entire process moot. In these situations, it would be mandatory to have post-marketing surveillance for all approved drugs lacking definitive scientific evidence.

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The Biopharmaceutical Report *is a publication of the Biopharmaceutical Section of the American Statistical Association. Layout designed and produced at the American Statistical Association, Alexandria, Virginia.*

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