

PERSPECTIVES

## Ethical Issues Regarding Fee-for-Service-Funded Research Within a Complementary Medicine Context

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### ABSTRACT

Ethical issues are presented concerning the appropriate use of a fee-for-service strategy to fund clinical research assessing preventive complementary medicine approaches, particularly the effectiveness of dietary supplements for disease prevention. Reasons for the need for such an alternative funding approach are identified and historical precedents are noted. Presuming *a priori* key desiderata of doing no harm, not taking advantage of the ill, and pursuing recognized useful purposes, six key ethical questions from the relevant literature are identified and discussed. Arguments are advanced that there is a sound rational, ethical basis (1) to ask patients to pay for clinical experimentation in the focused area of supplement-directed disease prevention; (2) to accept the reality that those who cannot pay may not participate; (3) to permit moderate profit from the ongoing research; (4) to allow researchers to receive fees for their support of such clinical research; (5) to pursue this alternative funding strategy in addition to conventional sources; and (6) to expect that patients can give informed consent in such settings. It is demonstrated that patient-funded research has been an integral component of clinical research for decades and that there is no inherent reason why explicit patient payment of fees need be less ethical than any other commonly accepted funding models. Accordingly, an ethical case is made for the appropriateness and value of significantly expanded fee-for-service-funded research within a complementary medicine context, particularly the assessment of dietary supplements for disease prevention.

### PROBLEM FOCUS

This commentary concerns the research area of preventive complementary medicine, particularly the growing interest in assessing the effectiveness of dietary supplements for disease prevention in apparently well individuals. We focus on the ethical issues concerning

the expanded use of a fee-for-service strategy to fund much needed rigorous clinical research (e.g., including informed consent, peer-reviewed protocol design, results analysis, and adherence to appropriate standards, such as those applied by institutional review board for oversight and human subjects use). Given the higher cost of long-term prevention trials in

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contrast to shorter term drug therapy treatment trials, an effective strategy for funding research in this area could be instrumental in helping to clarify the many questions and issues involved in the prevention domain. Moreover, expanded application of such an alternative funding approach is needed for several reasons, including:

1. The long duration of data collection before results accrue, resulting in high clinical trials costs;
2. Prevention trials frequently involve many confounding variables such as variations in reporting approaches to lifestyle and other behavioral changes, making such trials less likely to be definitive. Furthermore, with lack of agreement on how rigorous trial designs must be to demonstrate definitive results, prevention trials often demonstrate the need for further research rather than reaching any conclusion;
3. The inability to patent many products used in complementary medicine (e.g., natural ingredients) and the weak patent protection afforded to complex dietary supplement formulas, which results in low expectations of future profitability, making any long term research investment less attractive.

For these reasons, expanded approaches to funding research into the effectiveness of preventative complementary medicine, particularly dietary supplements, in disease prevention, would be potentially beneficial.

### FUNDING STRATEGY

Traditionally, patient-funded research, or what has also been called "fee-for-service"-funded research (Lind, 1996), indicates an arrangement whereby the patient or possibly a third party on behalf of the patient pays the investigator and/or the corporate sponsor for doing the research involving the patient. Certainly this practice is not new; Lind (1986) reported more than 14 years ago on "a for-profit company that was established to offer novel anticancer therapies on a contractual basis to patients who paid the appropriate fees, which ranged from approximately \$10,000 to

\$30,000 . . . " What we discuss in this commentary is a significantly expanded use of this fee-for-service approach with the following three criteria:

1. *Does no harm.* The research would focus on the efficacy of generally recognized as safe practices, particularly the use of nutrients, which pose little or no known threat, have a public history of safety, and are of moderate cost to trial participants.
2. *Does not take advantage of the ill.* The fee-for-service-funded research would necessarily not take advantage of the desperately ill or otherwise vulnerable (e.g., not as desperate) patient.
3. *Has a useful purpose.* The fee-for-service-funded research would have reasonable expectations of obtaining results that could usefully address questions of patient benefit.

### PRIOR EXTENT OF FEE-FOR-SERVICE-FUNDED RESEARCH

As Lind (1996) has noted, ". . . hard information is not available to document how often . . . patients [i.e., patients participating in clinical trials] . . . are asked to pay . . ." Data that are available suggest the practice may already be widespread. For example, a survey (Lind, 1987) of 104 randomly chosen hospitals (self-identified as 58 university hospitals, 7 research institutes, and 39 hospitals) asked, in part, the question, "Have any patients been asked to pay for experimental treatment (i.e., participation in clinical research) from the outset of an Institutional Review Board (IRB)-approved project? Survey results indicated that in 50% of the institutions, patients in one or more studies were asked to pay some fees from the outset of an IRB-approved project. Although these survey data are limited and difficult to interpret, they suggest that the practice of patient-funded research is prevalent. We note that historically any such fee-for-service-funded research would most likely have involved noncomplementary medicine approaches. With interest in complementary medicine rising significantly,

one could project a much greater incidence of fee-for-service-funded research in the future.

### SOME CRITICAL ISSUES

In reviewing the relevant literature, we address six questions regarding potential barriers to accepting an ethical basis for patient-funded research.

1. *Is it ethical to ask patients to pay for unproven clinical experimentation? In the face of uncertainty, should not the trial sponsor support the cost of the research?*

Critics against fee-for-service-funded research argue that the public should be insulated from being asked to support research experimentation, especially because some researchers may not always have the individual's best interests in mind. They argue that ill patients are vulnerable and can be exploited. We focus on research related to preventative complementary medicine, particularly with dietary formulations where the potential for harm is minimal. Numerous recent volumes are testimony to the growing body of knowledge of worthwhile and minimally harmful substances (see for example Lininger, 1998; Mindell, 2000; Murray and Pizzorno, 1998; Null, 1998; Shealy, 1998). Oldham's (1987) commentary is germane in this context as he argues, "Clearly, resources belong to individuals and if people choose to use their resources to fund research, who is to say that they should be prohibited from doing so? Our economic system allows people to spend their money on better nutrition, better housing, better sanitation, and better medical services. Would the critics of patient-funded research have those choices restricted?" Lind (1996) explains his support for fee-for-service research, stating, "Nor should we depend on drug companies to advance healthcare, since self-interest and internal politics govern their decisions. Asking patients to pay for experimental therapies under defined circumstances, specifically when an estimate of success can be honestly offered that allows the patient the opportunity to make an informed decision, may become an acceptable way to deal with the lack of alternative funding sources."

These authors make the case that in our economic system, individuals have the freedom to allocate their discretionary income as they choose, just as they may buy cleaner drinking water (e.g., with water filters), better health care services, etc., as long as they can make a rational and informed decision. Morreim (1991) notes, "Neither are the patients who want to pay for their own research inherently less rational or inherently more desperate . . . Indeed it could even be the case that patients funding their own research may be more inclined than others to demand adequate information on which to make a decision. They, after all, have something else at stake—money—and may have substantial extra motivation to insure that they are going to receive their money's worth." Morreim (1991) goes on to add, "reciprocally patients in conventional trials may find that the prospect of free drugs and medical care is a substantial, perhaps even exploitative inducement to participate." It would appear reasonable to conclude that there is nothing inherently unethical about patients participating in their own funded research. In response to those critics who argue that research often accrues benefits only to society as a whole, and hence no one individual should be charged, rich or poor, we note that complementary medicine in general, and dietary supplements in particular, are somewhat beneficial in their own right (Lininger, 1998; Mindell, 2000; Murray and Pizzorno, 1998; Null, 1998; Shealy, 1998), yielding a personal benefit to the participating individual.

2. *If entry into the clinical trial requires patients' financial capacity, are we denying access by the poor?*

We support the idea that all qualified candidates may enroll if they meet uniform eligibility requirements and can accommodate the fees for the services. However some critics argue that making entry contingent on fees actually precludes some participants. However, because we are by definition addressing clinical trials for which there is no consensus as to proven scientific benefit nor accepted health care, Morreim (1991) argues that "it does not follow that the poor are entitled to receive care that has not been judged to be a benefit." She

adds that, "we cannot espouse any automatic presumption that the poor, or any other societal constituency, are somehow entitled to be included in any and all research protocols." Because a clinical trial most often implies there are not yet data unequivocally recognized by medical science indicating a complementary approach, or some dietary supplement is efficacious, it can hardly be argued that all are already entitled to it.

3. *Is it ethical for the study sponsor, if it is an investor-owned company, to profit from ongoing research?*

Some argue that the presence of profit or gain taints any research initiative. In response, one notes that for-profit entities are embedded in every aspect of all types of clinical trials, past and present. Addressing this question, Oldham (1987) reminds us that, "Clearly, investor-owned hospitals already treat patients and carry out clinical research." The landscape has investor-owned corporations providing health care to millions everyday. He goes on to state that "conclusions that abuses and unethical behavior are *a priori* greater in the private sector than in traditional government-university-pharmaceutical company research arrangements are without foundation" (Oldham, 1987). Indeed investor-owned, for-profit health care is an unalterable component of our health care system and is involved in most non-governmental funded clinical trials. If we are to remain rationally consistent, there is no basis for the perspective that profit-orientation should be excluded from a role in clinical research.

Given that a profit may be made, the question is who should set the fees for participation, and how much profit? Because the company is ultimately responsible for the continuity of the trial, in the end it must set the fees, although this does not preclude input from an IRB, the company's oversight groups such as its Board of Directors, Scientific Advisory Group, etc. The difficult issue is more the level of profit, because the fees at the minimum must cover costs if there is not subsidization from outside. Business must recognize its role as an ethical and responsible component of the social order,

engaging in fair market practices. In addition, the nature of a "trial" indicates there are scientific questions about efficacy, and thus there is a natural price inhibition imposed resulting from the economic considerations of the product's probable "payoff" to the user. In the end, the fee level results from the economic equilibrium between the value the company would expect from therapeutic success and the probable expected payoff the well-population trial participants can calculate from their financial level of investment. Overall it is in a company's interest to keep costs as low as possible, thus making the entry fee as low and hence attractive as possible; this lowering of overall costs preempts accusations of inappropriate profiteering.

4. *Is it ethical for researchers to receive fees (beyond cost reimbursements) for doing clinical research?*

Critics argue that fee-for-service-funded research will undermine the prospects for honest research. However, the practice of receiving fees for clinical research is not only widespread, but also endemic in clinical research. For example, it has been noted that "Pharmaceutical manufacturers commonly contract with clinical investigators for premarket testing of new products. The per-patient reimbursement offered to the investigator generally exceeds the per-patient costs incurred by the investigator" (Shimm, 1991). Spiro (1986) gives the following example: "Take the controlled clinical trials of ulcer healing . . . drug companies pay generously for them . . . the shortage of ulcer patients is so great that the bounty paid for each one enrolled in a clinical trial has risen. I hear stories of \$5,000 per patient study completed or more." Higby (1990) also reminds us that "some federally sponsored studies . . . in fact pay investigators in direct proportion to the number of patients recruited into the study, as do many studies sponsored by pharmaceutical houses."

Lind (1986) points out that anyone who treats patients with experimental or even standard research treatment profits at least professionally, if not monetarily. He argues that certain high-profile clinical research is highly profitable—particularly to the clinical research facility it-

self: it brings in overhead charges, stimulates referrals, adds to the volume of patients through hospital facilities, etc. (Lind, 1996). Research in bone marrow transplantation and high-dose chemotherapy for breast cancer and other malignancies are typical examples. Lind (1996) states that "It is my view that it is impossible for the IRB to remove either the profit or the profit motive from research, not should such be attempted." If we accept the necessity of clinical research, we must accept the presence of some sort of reimbursement to the researcher.

5. *Why not use traditional sources (e.g., National Institutes of Health (NIH) National Cancer Institute, pharmaceutical companies, etc.) to fund research?*

It has been argued that there are ample traditional funding sources that may be tapped, such as the NIH. Although the NIH does indeed fund some limited studies, the relative costs of the research we are discussing and the range and extent of potentially rewarding areas for investigation compared to the NIH total budget clearly indicates that only the smallest fraction of research in this area can be addressed by federal funding sources. Some critics suggest that for dietary supplements the pharmaceutical industry can shoulder the burden, even recognizing the lack of patentability of the constituent approaches or dietary elements, because if the results are potentially commercially viable, the pharmaceuticals will pursue these prospects. This observation begs the question because it is precisely the fact that the cost of the trial likely overwhelms the expected potential revenue that precludes any consideration of this research domain by many pharmaceutical companies. Therapies for disease prevention are likely to be optional and nonprescriptive; such prospects undermine expectation that a pharmaceutical could hope to ever recoup research investment costs. Other critics may point to the currently ongoing Harvard Physicians' Drug Trial II study, testing whether vitamin supplements prevent cancer and other chronic diseases, an example of the kind of study we are addressing, and note it is funded by the commercial firm BASF AG (Lud-

wigshafen, Germany). This indicates it is not inconceivable that we may see extremely rare examples of a commercially funded altruistic effort.

The use of vitamin C, E, a multivitamin, and  $\beta$ -carotene being tested in this trial is by definition not going to provide a patentable product if one of the combinations or just a single ingredient proves useful. Thus extremely rare, altruistic commercial funding does occur, but it can hardly be a model for the widespread testing that is needed over hundreds and hundreds of possible tests that can and should be run.

Morreim (1991) states that, "our usual reservations against permitting, let alone requiring, patients to pay for their own research may have to be modified in light of the ever tightening availability of research funding . . . it seems evident that it may be quite appropriate to permit patient-funded research." In addition, particularly in the more disputed research domains such as alternative medical therapies or the benefits of nutraceutical dietary supplements, funding can be extremely modest at best. However these low-cost, safe approaches may be very attractive additions to our medical armamentarium. Oldham (1987) indicates that, "A private sector enterprise that is created to meet the needs of patients with cancer and their physicians by allowing more access to emerging biotechnological advances may be very useful." Given the pressures on the traditional governmental agencies and the influence of political pressures and set-thinking by peer-review grant committees, many innovative areas can be expected to languish unless new funding sources, such as patient-funding, are ethically tapped.

6. *Are patients who are asked to pay able to give adequate informed consent?*

Some argue that when people are desperate or ill, they cannot really give informed consent, and researchers may take advantage of them. We certainly recognize this danger. However, we are specifically addressing prevention among healthy individuals, or those for whom no current orthodox prevention is accepted by the medical-scientific community. Some critics

argue that all consumers need protection, often because they are ignorant. Thus, the unregulated opportunity to pay will lure unsuspecting individuals into clinical trials. Because we are not dealing with sick people and because informed consent is one of the given criteria above, the question becomes whether the public can be trusted to fairly assess its own best interests in the area of complementary medicine, particularly dietary supplementation, for disease prevention. It would be logical to expect that such assessment of self-interest would be most likely in a fee-for-service context. As Morreim (1991) sums it up, "Patients who wish to fund their own research are not inherently more vulnerable; the conflicts of interest borne by these researchers are not necessarily worse than the conflicts permeating the rest of clinical research. . . . " Oldham's (1987) response provides a succinct summary regarding this question: "There is no compelling reason to believe that patients who fund research on their own behalf are less informed and thus less able to give proper consent. Although the objection has been advanced by some that paying for research compromises the ability to give informed consent, there is no data or rational argument otherwise to support it."

In summary, patient-funded research has been part of the clinical research context for decades. In reviewing issues raised regarding overt patient-funded research, there is no inherent reason why explicit patient payment of fees need be less ethical than other commonly accepted funding models. Thus a strong, ethical case may be made for the appropriateness and value of significantly expanded fee-for-services-funded research in assessing the effectiveness of dietary supplements for disease prevention in healthy individuals.

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