Financial ties as part of informed consent to postmarketing research

Attitudes of American doctors and patients

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Postmarketing research, often called phase IV trials, is intended to familiarise doctors and patients with newly approved drugs. La Puma and colleagues, in Chicago, studied doctors' and patients' attitudes to whether doctors should receive payment for taking part in such research. We asked for commentaries on their findings from four ethical experts, who put the study in a British context, present the views of patients, and examine some methodological assumptions.

The attitudes of doctors and patients about financial ties as part of informed consent to research have not been studied. Neither the United Kingdom's quadripartite regulations[1] nor new research guidelines in the United States[2] require financial disclosure to patients.

Postmarketing (phase IV) research is part of the $10.9bn the American pharmaceutical industry spends annually on research.[3] Ordinarily uncontrolled observational cohort studies of outpatients,[4] phase IV trials are often intended to familiarise doctors and patients with new drugs approved by the Food and Drug Administration. In the United States phase IV trials and postmarketing surveillance (seeding studies) are generally indistinguishable.

Industry sponsors pay doctors to enrol their patients and to collect dosage and effect information. Patients may receive the new drugs free; doctors may also receive payment for laboratory examinations and office visits. Yet patients may be unaware of their status as research subjects.

Methods

To understand patients' and doctors' attitudes about these arrangements, we developed structured, parallel, self administered questionnaires to gather data on attitudes about informed consent to, financial disclosure about, and participation in postmarketing research. The questionnaire for doctors was pretested and validated and then distributed to all active staff physicians (n=733) of a large, suburban, community teaching hospital.

The questionnaire for patients was pretested and validated, and then distributed by a research associate to consecutive patients (n=269) in a general medical office. Patients under 18 years of age and those who seemed to be acutely ill were excluded (n=29).

Participation was voluntary and confidentiality was assured. The institutional review board of Lutheran General Hospital approved the research protocol.

Results

Of the 733 doctors surveyed, 394 (54%) responded. Age in years (mean 45·4 (SD 11·5)) and sex distribution (79% (297) male) of respondents did not differ from that of the staff as a whole. Respondents had been in practice for 1-60 years (mean 14·6 (11·1)) and represented all clinical departments.

Of the 269 outpatients approached, 200 (74%) returned completed surveys. Respondents ranged in age from 18 to 87 years (mean 49·7 (16·9)). Most were female (64%; 123), in excellent or very good health (53%; 103), and had a regular doctor (85%; 167). Twelve (6%) had been part of a research study on a new drug.

One hundred and forty four doctors (36%) had been asked by a drug company to enrol patients in a phase IV trial. Of the 106 (27%) who had participated, 79 reported whether and how much they had received for each patient enrolled. Forty one of 79 (52%) reported that they had not been paid a fee; three wrote in the margin that a programme, institution, or employer had accepted the fee for them. Thirty eight reported that they had been paid from $5 to $5000 (median $80) for each patient enrolled.

Most doctors (64%; 240) found it acceptable to be paid a fee, while most patients (56%; 110) found a fee unacceptable ($P<0·005$). Proportionately fewer doctors (75%; 282) than patients (86%; 171) believed that a physician should inform a patient if the physician is paid for enrolling the patient ($P<0·005$) (table).

Responses to questions about investigators' financial ties to research sponsors

	% (No) responding "yes" or "probably yes"*	
	Patients (n=200)	Physicians (n=394)
When a doctor asks a patient to participate in a research study, should he/she tell the patient:		
What company, agency, or foundation is paying for the study?	92 (183)	85 (328)
Whether he or she owns stock in the sponsoring company?	78 (155)	74 (277)
Whether he or she is paid a salary by the sponsoring company?	81 (159)	78 (295)
Whether he or she is paid a fee for each patient enrolled?	86 (171)	75 (282)†

*Some subjects did not respond to all questions. †$P<0·005$.

Respondents who found fees acceptable were asked how much, over the direct costs, the doctor should be paid to enrol each patient. Ninety five doctors made this estimate, most frequently suggesting $100 (range $10-$2500, median $100). Patients who made this estimate (n=31) answered $10 most frequently (range $10-$100, median $15).

Most responding doctors (67%; 253) and patients (69%; 133) thought that some doctors might be influenced to enrol patients just for the fee.

Discussions

Moral questions of dual loyalty, research purpose, truth telling, and informed consent for phase IV investigators raised by these data have been explored briefly elsewhere.[5,6] We know of no data which suggest that doctors actually include their remuneration for research as part of the informed consent process. Indeed, doctors who inform patients may encounter resistance to enrolment.

Conclusion

Doctors and patients disagree about whether remuneration of doctors is acceptable in phase IV research but agree that information about financial ties

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to the research sponsor should be part of informed consent. Such information would make explicit a part of the conflict of interest that confronts doctors who are simultaneously clinicians and phase IV investigators receiving enrolment fees. Whether disclosure is enough to extinguish doctors' conflict of interest in post-marketing research provides opportunity for further study.

These data were presented at the 16th annual Society for General Internal Medicine national meeting in Washington, DC, 1993; the 7th annual Society for Medical Decision Making national meeting in Triangle Park, North Carolina, 1993; and the 5th annual University of Chicago McClean conference in clinical medical ethics in Chicago, Illinois, 1994. The work was funded in part by the Lutheran General Hospital and the Lutheran General Medical Group. The views expressed in this paper are those of the authors and do not necessarily reflect the views of the supporting institutions.

1 Joint Committee of the ABPI, BMA, CSM, and RCGP. Guidelines on postmarketing surveillance. *BMJ* 1988;296:399-400.
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5 La Puma J, Kraut J. How much do you get paid if I volunteer? Suggested institutional policy on reward, consent, and research. *Hosp Health Serv Admin* 1994;39:193-203.
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Into a British context

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The study by La Puma *et al* considers two questions of ethical and practical importance: should doctors be paid for recruiting patients to postmarketing surveillance studies, and should patients be informed about a doctor's financial incentives for recruiting them?

The doctors and the patients held somewhat different views. Most patients thought that their doctors should not receive a fee, while most doctors thought it acceptable. The differences were partly of degree—patients judged that a reward could be $10, but doctors thought that $100 was reasonable. A majority of both groups believed that potential subjects should be told of financial incentives.

The study can be criticised on four main points. American views on free information are not identical to British ones. Many doctors failed to reply to the questionnaire, and their views may have been different from those expressed in the study. Estimates of "reasonable" fees were based on replies by only a few doctors and patients. And questionnaires can give questionable answers to practical problems.

How do we put the results into a British context, and what should we do?

There have been problems with postmarketing surveillance (phase IV) studies in Britain,[1] and the new safety assessment of marketed medicines (SAMM) guidelines[2] are intended to make such studies more informative and less open to accusations that they are merely a marketing ploy.[3] The guidelines stipulate that reference to a research ethics committee is required if patients are to be approached for information, additional investigations are to be performed, or it is proposed to allocate patients systematically to treatment.

The provisions in the guidelines bring almost all worthwhile studies within the ambit of research ethics committees. We should accept that unsystematic and superficial studies, which are susceptible to accusations that they are disguised marketing, be treated as such—they "are unlikely to provide either reassurance that a drug is safe or sufficient evidence to indicate reliably a safety hazard."[3]

It is, then, for ethics committees to decide how they tackle the problems posed by La Puma and colleagues' questions. Because both doctors and patients are keen to see some declaration of financial interest, the investigator should at least be asked, when applying for ethics committee approval, to stipulate what he or she is being paid. The committee could agree in advance what constituted a payment sufficiently large that it might modify the doctor's behaviour. Small payments would not need to be declared to prospective subjects, but if the payment were above a certain sum it would be obligatory to mention on the consent form that the doctor was receiving a fee. Doctors and lay members together ought to decide what would be a large enough sum to warrant mention.

This would help to reassure patients that they are not being asked to take part in a study solely so that the doctor can make money, and it would allow doctors some consideration for the time and effort that they put into recruiting patients for worthwhile studies.

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From the patient's perspective

Julia Neuberger

Payment for phase IV research was a major issue when I was surveying the work of research ethics committees in the United Kingdom. Many doctors argued that patients need not be told if the researchers were being paid. This was on the assumption, within hospital based research, that the money earned would go into institutional or research funds. Lay members of research ethics committees were less clear, arguing that it might be right for research subjects to be told, but the fact that research funds would be enriched by the individual patient's participation might be felt as additional pressure to participate. Most phase IV studies, however, are conducted by general practitioners. Not all such studies even go to a research ethics committee, let alone provide full information for patients.

If one accepts the principle of patient autonomy, it does not seem right to keep from any patient the details of the amount that a doctor researcher is being paid to recruit patients into a study. A patient is a free moral agent and can make the decision to participate or not to participate in a study to further human knowledge. But the fact that a pharmaceutical company is funding the study may indicate that the study is not entirely for the purpose of furthering human knowledge. Post-marketing information is of great interest to the industry itself, since side effects that are discovered may prove expensive. Such an investigation is also clearly of interest to patients, who might wish to avoid such side effects.

So it is a complex debate, but one in which the principle of honesty must win out. If doctors are to be