Who has the Ultimate Responsible for Publishing Clinical Research Results?

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Thailand has become a fertile soil where international pharmaceutical companies clamor to try out their latest products in phase II, III and mostly IV trials. These activities have had some beneficial effects for the Thai academic community as funds have come in to supplement low government salaries and investments have been made in new computers and often badly needed additional laboratory apparatus. Young and not-so-young investigators have been able to attend international conferences and eat fine meals in good hotels. There are, however. some risks attached to doing commercially sponsored research. Worldwide, a few excellent scientist's reputations have suffered when they became identified as "professional drug testers". Much of their work then becomes suspect and not likely to be accepted by first-rate international peer review journals. Their research may then be viewed with some reservations by regulatory agencies such as the US-FDA and the scientific community at large. Clinical research is expensive, even when done in a developing country. The company sponsor is not doing studies as a charitable service, but expects results that will help them gain FDA approval of the product and, eventually, profitable sales in Thailand. Furthermore, extensive human studies have already been done in the country of origin by the time they come to Thailand. This is required by international convention and also by our local ethics committees. Results are therefore often predictable. The sponsor is not likely to expect surprises such as previously undetected negative results. He is even less likely to encourage their publication if some are indeed found. Thus, it should not be surprising for an industrial sponsor of a study to ask the Thai clinical research team to sign a statement that would prevent them from publishing any results, unless the manuscript has first been approved by their home office's scientific, legal and marketing officers.

Let us now assume a hypothetical situation where you have tested a new NSAID designed for the treatment of osteoarthritis. It is already on the market in Europe, having been approved by several FDAs. Repeat clinical trials in Thailand where done because they were required for submission to the Thai regulatory authorities to gain approval for marketing the drug in this country.

Key word : Ethics, Researcher

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J Med Assoc Thai 2001; 84: 1217-1220

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You have now found that the drug works well but causes an unacceptable incidence of interstitial nephritis in Thai patients. You have signed an agreement not to publish unless the manuscript is approved by the European company sponsor and he is not happy with your paper. What should you do? Not publish your data and conclusions or leave out the adverse findings? You may, perhaps, be told that interstital nephritis has not been a problem in European patients and that your data are not relevant or only applicable for Thai patients who eat to much pepper oil or paracetamol. The company has now decided not to seek Thai FDA approval after all and burry your paper. If the sponsor is a truly ethical company, of which there are many, he would congratulate you and let you publish the results and conclusions, as you indeed must, as interstitial nephritis is serious business. We once had an experience with unexpected adverse data and, fortunately, learned that we were dealing with an ethical and highly responsible industrial sponsor who actually added his name to our paper and thus gained much international credibility. It is, however, best not to be placed in a position where one might have to face a less pleasant outcome than in our case.

What then is the best and correct response to a request for signing an agreement not to publish results of clinical research without prior approval from the sponsor. You must first decide what is your own position in this enterprise and answer to yourself and your academic colleagues whether you are an independent scientist-investigator or whether you are a contract employee of the company sponsoring the research. If the latter is the case, you would quite correctly be obliged to protect company interests and would have to agree not to publish at all at the start. This situation arises mostly in phase I and perhaps II trials where it is not at all yet clear whether the drug will ever reach the market and actual clinical use. You would then, however, be morally and professionally obliged to stop the study once you recognize that there are unexpected adverse events. Whether it is ethical to withhold serious adverse events from the general scientific community if the product is actually marketed, is another moral and legal issue. We have not encountered this problem and will do our best to avoid it. It is suggested that the researcher carefully documents adverse events and saves copies of all records in his personal files for future review. An ethical company would have to submit your adverse report if and when they ask for approval of the product from their regulatory authority (FDA etc). If they do not, and the product later appears on the international market without appropriate warnings, you would have the option and perhaps duty to publish your results in defiance of your employer company and any prior agreements that you may have signed with them. It would, however, be wise to discuss this with an attorney experienced in such matters.

If you decide that you will remain an independent clinical investigator, you must keep in mind that: 1) Clinical research is carried out to identify efficacy, safety and advantages over older therapies of new products. 2) It must identify any adverse side effects and, above all, must be carried out independently by a team that has no financial or other vested interests in the product or its manufacturer. Regulatory agencies, such as the US-FDA and counterparts in other major countries, do not consider "in house" clinical studies as having the same power as those carried out by reputable independent investigators. Study protocols that contain a clause prohibiting the investigators to publish without company approval, may move the study from independent to the "in house" category. This, obviously should not even be in the interest of the sponsoring company. Respected professional organizations such as the American College of Physicians, American Medical Association and others[1-6] have published guidelines for investigators which, if followed, will help them retain their integrity and independence. Furthermore, the most respected peer review journals require the investigator to declare any dependency or partiality to the product or sponsor. Signing an agreement that the investigator might be compelled to withhold relevant data at the request of the sponsor, could be interpreted as loss of impartiality.

How does one then handle a sponsor who presents you with a study protocol to sign which contains a restrictive paragraph regarding publication? We have encountered this on several occasions and coming from internationally highly respected pharmaceutical firms. These restrictive paragraphs usually originated from the legal and marketing staff of the company and not their scientists. They were quickly removed when we declined to

sign such documents and countered that we will submit any manuscript for criticism to the company medical staff before we send it to a publisher, however, we retain the final authority whether to publish or not.

Thailand's medical centers are now carrying out an ever increasing number of clinical trials. We would like to maintain our reputation as honest and competent investigators. This depends to a large degree on mutual trust and our individual reputations among editors of peer review journals and the regulatory agencies that ultimately approve or disapprove a new drug. It is therefore important that our colleagues do not succumb to financial and other incentives and become professional "drug testing factories" and thus become known as agents of the sponsoring firms and not as seekers of truth and servants of the public.

(Received for publication on May 23, 2001)

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