CASE STUDY

# A clinical trial in a developing country: many questions, few answers

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I [SK] am the chairperson of the review board of medical ethics research involving human subjects at the Faculty of Medicine, Thammasat University, Thailand. On a number of occasions our committee found it difficult to make a decision, so I would like to put forward a case study for discussion to have opinions of other experts to help us make better decisions.

The study is proposed as part of a multicentre study of a new antihypertensive drug already licensed in a western country. The sample size would be 140 cases. The study would be carried out in up to 20 centres in Asia with each centre studying seven cases. The drug company would provide a protocol for every country to follow, which contains instructions in English but very little translation in our language. The company would provide some money for the researcher. The review board is informed that other centres have already approved the proposal. Researchers would not be permitted to analyse the data but would have to send it all to the drug company who would analyse the data. There would be no meeting of researchers nor would there be instrument standardisation, etc.

Our concerns are as follows:

1. What could our young researchers learn from these kinds of projects as the protocol will be prepared, analysed and interpreted by the donor agency?
2. Does the drug company really intend to learn about the efficacy and side-effects of the drug in Asian people and whether it is different from that in westerners? Or is it some sort of an advertisement?
3. Could seven cases in each centre be enough to eradicate human bias, instrument bias, time of measurement bias, position of the patient, age, sex, individual, lifestyle and many other biological biases?

Any response would be most appreciated as we have had many protocols like this coming through our committee.

## Response 1: Unscientific and therefore unethical

I cannot offer any comments on the scientific nature of the proposed study since protocol details are not available. If a study is technically not sound, it is also unethical. I hope the ethics committee has access to the full protocol. However, it is difficult to understand the logic of having seven cases each in 20 centres, particularly for a common condition like hypertension.

Second, it is not clear why money should be given to researchers. Is it for their time and expertise or is it an inducement? What type of analysis do the researchers want to do? Is it a double-blind study?

Informing the ethics committee that other centres have already approved the study would amount to pressure tactics. In any multicentric study, standardisation is obligatory.

I have raised several questions for clarification. However, based on the available information given by Professor Kietinun, such practices followed by drug companies are deplorable and deserve to be condemned.

M D Gupte

## Response 2: Caution is required

The proposed trial raises two important issues and is typical of the kind of clinical research that is done in developing countries. Many countries (including India) have a provision that requires the drug controller to ask for data on clinical trials in the country even if the drug has been approved in other countries. The rationale for such a provision is obvious: to look for data that would factor in local conditions such as dietary habits, lifestyle, etc. This is of particular importance in the case of drugs for chronic illnesses as these have often to be taken lifelong. Unfortunately, such trials are often seen as mere formalities to satisfy regulatory requirements.

Traditionally, the pharmaceutical industry needed the academic community to do clinical trials, and the latter was the key partner in such trials and took decisions regarding protocols, sampling, design, etc. Contrary to this, in the last decade, we have seen a shift where the industry employs or enrols physicians to do drug trials that are controlled by the industry. Along with this role reversal, we also see a growth of contract-research organisations (CROs) that undertake research on behalf of the industry (1). As multicentre trials involve a large number of sites and investigators, pharmaceutical companies now prefer

to contract out research to such CROs.

The second issue is the design of the trial, a rough idea of which we can get from the sample size proposed—140 subjects in 20 centres. Phase III clinical trials are designed to evaluate the effect of a new drug on clinical outcomes that are of relevance to the patient such as death, disability, etc.—which may be called 'disease end-points'. Such trials require many participants and need to be followed-up for a long time. For example, the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) involved 40,000 hypertensive patients followed-up for 6 years (2). Thus, it may take up to a decade or more to get reliable data about the effect of drugs on disease end-points. There is an attempt to design trials that 'short circuit' this lengthy process by using what are called 'surrogate end-points'. These trials evaluate the effect of a drug not on the eventual outcome, but on specific markers such as blood pressure, cell count, laboratory results, etc. Such trials, typically, may involve around 100 patients and could be concluded in a few months. The logic for doing so is that these markers are fair indicators of the final outcome.

Unfortunately, this is often not true. Such short-term studies indicate that the level of certain risk factor(s) are reduced but do not throw enough light on the eventual outcome. For example, it has been estimated that to prevent one cardiovascular event in a year, 120 elderly patients have to be treated for that same period. Most treated patients will actually receive no benefit. If there are unanticipated adverse effects, even relatively uncommon ones may minimise or eliminate the average health benefits from drug therapy. But such adverse effects will not be picked up by trials that only look at, say the effect of a drug in lowering blood pressure.

For example, a large trial showed that low-dose diuretic therapy was associated with a reduced risk of coronary heart disease, but this was not true for high-dose diuretic therapy or beta-blocker therapy(3). But all three regimens lowered blood pressure. Thus, there is the possibilty of achieving an incomplete or misleading evaluation of a therapy when surrogate end-points are used to assess therapies.

This does not mean that short trials using surrogate end-points are of no value. When combined with observational data about disease end-points they can be of value. If a drug has already been evaluated adequately, such trials can be used to generate additional data in different locales. However, given the relatively uncertain significance of the outcomes of such trials, results should be treated with extreme caution if they are sponsored by pharmaceutical companies and the data are not available for independent evaluation.

Amit Sengupta

## References


1. Bodenheimer T. Uneasy alliance—clinical investigators and the pharmaceutical industry. 2000;**342:**1539–1544.
2. Davis BR, et al. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Hypertens* 1996;**9:**342–360.
3. Psaty BM, Weiss NS, Furberg CD, Koepsell TD, Siscovick DS, Rosendaal FR, et al. Surrogate end points, health outcomes, and the drug-approval process for the treatment of risk factors for cardiovascular disease. *JAMA* 1999;**282:**786–790.