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Responding to deaths during a clinical trial

The deaths of patients during clinical trials conducted by the All India Institute of Medical Science (AIIMS), New Delhi, revealed under the Right to Information Act (RTI), made news in most leading newspapers in India (1,2,3,4,5). The government has asked for a high level enquiry into the deaths (2,4) which may help in re-establishing public trust in ethical research. In the interest of continuing medical research, some issues such as questioning the authenticity of ethically approved clinical trials and the use of the RTI Act need further discussion.

The ethical conduct of a clinical trial does not end with the formulation of a study design and obtaining a signature on an informed consent form. Fatal adverse experiences for subjects in clinical trials should be scrutinised. But, certainly, there are difficulties in establishing the cause of death when interpreting the data retrospectively. It is not easy to attribute risk of death to the trial drug/vaccine, and it is even more difficult to rule out its possible contribution.

Other confounding factors may play a vital role in determining the final outcome. Increased mortality may be attributed to the natural course of diseases such as encephalitis, Gaucher disease, or advanced HIV/AIDS in the study populations that are generally associated with poor outcome. In such circumstances, it is highly probable that the control arm might have a higher death rate than the treatment arm. Also, we should consider the mortality rate among all subjects under trial instead of the absolute number of deaths. In a large study, this number may not have much impact when compared to the natural outcome of the diseases. In addition, death rates in the trial may be compared with the rates achieved in other similar reported clinical trials in order to rule out any causal relationship of the trial drug with mortality.

It is ethical to involve infants in trials provided there is minimal risk, which is defined as no more risk than can be expected in the normal protected environment of the child (6). If it is found that the hypothesis on which the trial is based is beneficial, at least half the subjects in a randomised controlled trial may benefit while those in the control arm will be no worse off than if the research had not been done (7).

However, any breach in ethical conduct of a clinical trial should always be evaluated. New rules for clinical trials were implemented in 2005 (8) probably due to the demand from multinational drug companies and organisations. It has become easier and more cost-effective for western countries to conduct clinical trials in India rather than in their own countries, which have strict regulations, complicated safety and compensation requirements and a smaller study population.

India's vast genetically diverse population with plentiful research subjects, its favourable economic conditions, cheap labour and low infrastructure costs have accelerated the process (8,9). In addition, a considerable number of trials are industry-sponsored trials of pre-approval therapies which are largely focused on defining indications and marketing strategies. Hence, it becomes of utmost importance to protect the most vulnerable subjects in a trial. At the same time, it is difficult to judge what constitutes sufficient grounds for disqualifying a research investigator from conducting human experiments.

The Randomised Control Trial (RCT), begun in the mid-20th century, probably ranks as one of the most important milestones in the history of medicine. It is because of RCTs conducted over many decades that we are able to use a wide variety of safe drugs today. They are among the most reproducible and valid forms of research and rely on randomisation and unbiased evaluation of outcomes (based on placebo controls and "hard outcomes" such as patient death) to minimise errors (10). RCTs usually have built-in safeguards and external oversights and audits, all of which protect against serious biases.

Both doctors and patients are aware that no drug is free of adverse effects. Safety and adverse effects are inversely related to each other. The degree of balance between the two determines further acceptability for human use. We believe that most reputable clinical trials investigators, particularly in government academic institutions, are careful to ensure the integrity and credibility of their work. Moreover, to the best of our knowledge, there are virtually no studies which have derived information prospectively in individuals who have died during clinical trials.

Interrogating honest investigators who are primarily interested in expanding knowledge and research may result in undue stress, leading to their refusal to conduct future trials. We must protect patients enrolled in clinical trials, but we must find better ways to protect professionals also. If we do not, the progress of medical research in India may come to a standstill, particularly in controversial and distressing areas (11).

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