Balancing Professional Ethics

CASE COMMENTARY

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Before commenting on some of the ethical issues raised by this case, one has to note that certain details about the trial are not clear. For example, it is not stated whether this is a multi-centre trial, but one may assume it is. It is also not clear whether the serious adverse events reported recently are from this centre or from other centres. The main ethical issues causing concern are:

1. The recent reports of serious adverse events "possibly related" to the trial drug XTX007.
2. The request from Mrs L to be included in the clinical trial when she did not satisfy the inclusion criteria.
3. The payments made (and promised) to the principal investigator by the pharmaceutical company sponsoring the trial, over and above the fee paid to the principal investigator's institution for costs incurred in conducting the study at the institution.

These three issues not only concern the principal investigator (PI), but raise questions regarding the approval presumably already given by the ethics review committee that reviewed the trial protocol.

We are told that the central data safety monitoring board (DSMB) has asked to increase the intensity of surveillance because of recent reports of serious adverse events (SAEs) "possibly related" to the trial drug XTX007. The SAEs reported include more than one incident of cardiac arrhythmia, acute myocardial infarction and acute liver dysfunction. The ICH-GCP guidelines require that all SAEs should be reported immediately to the sponsor, followed promptly by detailed written reports. In addition, the investigator should also inform the drug regulatory authorities and the ethics review committee, so that they may take appropriate action.

Considering the seriousness of the adverse events reported, it is surprising that the DSMB merely recommended increasing surveillance and did not advise suspending the trial until further investigations are done. The principal investigator, however, has the responsibility of ensuring the safety of research participants, and should suspend the trial immediately because the adverse events reported are life-threatening and not acceptable. The Helsinki Declaration states that physicians should engage in research involving human subjects only if they are "confident that the risks involved have been adequately assessed and can be satisfactorily managed", and only "if the importance of the objective outweighs the inherent risks and burdens to the subject." In this trial, the objective is to treat the symptoms of constipation in irritable bowel syndrome, and the potential benefits from the trial drug clearly do not outweigh the risks of the SAEs that have been reported.

One also cannot help wondering whether the independent ethics review committee (ERC) that approved the protocol had conducted an adequate scientific review, such as a careful examination of the relevant scientific literature, and looked for evidence of laboratory abnormalities and results of animal experimentation with the experimental drug. If adverse events similar to those reported had occurred in phase I and phase II studies in humans, the ERC should not have given approval for a phase III controlled clinical trial, in which the potential benefit (relief of constipation) does not justify the risks associated with the new drug (cardiac arrhythmias, myocardial infarction and liver dysfunction).

Regarding the request made by Mrs L, the fact that she has had viral hepatitis three months before (one of the exclusion criteria) clearly disqualifies her from entering the trial. Mrs L has requested the PI to ignore this disqualification and to include her in the clinical trial, because she thinks it is the only way she can get the new drug which may relieve her symptoms of constipation. While the principal investigator (PI) would naturally want to do what is best for his own patient, including giving her the chance to get some relief from the potential benefits of the new drug, the PI should not deviate from the protocol that has already been approved by an independent ERC according to accepted scientific and ethical principles. In addition to complying with the principle of scientific integrity, the PI, with his knowledge of the reported SAEs, should be guided by the ethical principle of non-maleficence, which should prevail over a possible beneficence. The PI should explain to Mrs L the possible serious adverse events that could occur with the drug, particularly in view of her past history of liver disease, and that even if she were to be recruited, she may not actually get the trial drug if she was randomised into the placebo group.

Another important aspect of this case is the ethical issue of conflict of interest arising from the financial incentives offered to the principal investigator by the

pharmaceutical company sponsoring the trial. In my view, the $800 paid to the principal investigator for each patient recruited to the trial is far too excessive, and any payment to the PI for recruiting patients to the study may not even be indicated, considering the fact that the institution where the PI is employed is paid a fee for the costs incurred in conducting the study, such as the use of facilities and materials and also for professional services. An independent ERC in Sri Lanka would not have approved such a sum to be paid to the PI. The promise of a bonus payment of $5,000 to the PI for achieving a recruitment target of 40 participants is clearly unethical and should not have been approved by the ERC. Such an incentive can definitely lead to a financial conflict of interest and the possibility of compromising scientific integrity as well as patient safety, and the PI should not have agreed to it.

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