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## Innovations in monitoring of adverse drug reactions: the role of a technical advisor

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*To undergo treatment you have to be very healthy, because apart from your sickness you have to withstand the medicine.* – Molière

### Abstract

Adverse drug reactions (ADRs) have ethical implications. These include assessment of the risk–benefit ratio and re-administering informed consent based on the new ADRs identified. The Indian Council of Medical Research ethical guidelines mandate the scrutiny of ADR; and the standard operating procedures of the ethics committee of the authors' medical school endorse this line. However, institutional review board members are often hard-pressed for time and are unable to analyse all the reported ADRs as thoroughly as required. This calls for a dedicated system for the scrutiny of ADRs. This paper seeks to share the experience of development and implementation of a review mechanism for ADR monitoring.

The authors report an innovation in ADR monitoring by appointing a technical advisor on ADR (TA-ADR). During routine assessment, an unusual occurrence of ADRs was noticed from internal and external sites which were related to the study drug, which in turn resulted in the trial being put on hold. This system is being reported here for possible adoption by others.

### Introduction

An essential part of the agreed mandate of all human ethics committees is the protection of the human participants. According to the Indian Council of Medical Research (ICMR) guidelines, "an adverse event (AE) or an unexpected adverse drug reaction (ADR) requires expedited review by the ethics committee" (1). ADR monitoring during clinical trials involving investigational new drugs (INDs) plays a critical role in ensuring the safety of participants. In addition, safety monitoring by

the ethics committee is important for making an ongoing estimate of risk–benefit, and hence has a bearing on ethical dimensions of the trial as well. If the risk–benefit ratio is found unfavourable, reassessment needs to be done based on the four moral principles of justice, autonomy, beneficence, and non-maleficence and re-administering of informed consent by informing research participants about potential ADRs based on the new problems identified. In spite of this overarching importance of ADRs and safety monitoring, this activity does not receive sufficiently thorough and comprehensive attention and review. One of the major reasons for this is the fact that members of the ethics committee have dual affiliations, one with their respective primary departments and the other with the ethics committee. AWHO document titled *Pharmacovigilance in drug regulation* observes that routine review of safety information requires considerable resources, expertise, support and commitment from those involved (2). Too much and uncritical reliance on data safety monitoring boards also dilutes the attention that ADRs deserve.

A systematic evaluation of the ADRs reported by the principal investigators (PIs) as per the norms recommended by the International Conference on Harmonization – Good Clinical Practices (ICH–GCP) (3) and in the format prescribed by the Council for International Organizations of Medical Sciences (CIOMS) (4) and Central Drug Standard Control Organisation (CDSCO), India, (5) is necessary. The ICMR ethical guidelines (1) and the standard operating procedures (SOPs) of the Institutional Human Ethics Committee (IHEC) of the authors' medical school mandate the scrutiny of ADRs.

Against this background, the Institutional Review Board (IRB) conducted a review of the Committee's structure and functions. The report on the review exercise recommended that a technical advisor (TA) on ADR monitoring (TA-ADR)

be appointed by the IHEC to exclusively scrutinise ADRs. The suggestion was accepted by the IHEC and the head of the institution. The office of the TA on ADR monitoring is an office of non-profit, like that of the chairperson and member-secretary of the IHEC.

A pharmacologist trained in pharmacovigilance took over as technical advisor to the IHEC on adverse drug reactions (TA-ADR) in the authors' institution in February 2010. He was not a member of the IHEC. He had signed a confidentiality agreement with the IHEC and was invited to its full board review meetings to report and offer clarifications on ADRs. We believed that it would have been more appropriate to have given this task to a pharmacologist, because not only would his/her task in the ethics committee be well-defined and focused only on adverse reactions and events, but his/her specialisation in pharmacology would give him/her the subject expertise to explore the adverse events and their causation based on pharmacokinetics, pharmacodynamics and other mechanistic points of view. IRB members are very busy going through the study protocols assigned to them and cannot give their full time to IRB work, due to the pressing schedule in their home departments. Therefore, we appointed a pharmacologist with a year's experience in pharmacovigilance as a TA-ADR.

We give below one of our experiences to highlight how this practice was useful.

The TA-ADR starts conducting close scrutiny of ADRs received periodically by the IHEC and prepares periodic reports. All the ADRs are entered into the computer according to the clinical study. The WHO causality assessment scale is being followed for assessing the ADRs (6). The reports are then periodically submitted to the ethics committee.

During routine assessment, an unusual occurrence of ADRs was noticed in a particular phase III clinical trial (Study X) of drug XYZ (names changed to maintain anonymity) for which approval was granted in June 2009. The Study X file had ADRs reported from the institution's site apart from the external sites. In April 2010, seven cases of osteonecrosis of a specific region (name withheld to maintain anonymity) were reported from the external sites by the sponsor of this study. According to the investigators, five cases were possibly related to the study drug XYZ and two were not. Apart from these reports, one report each of ischaemic colitis, ischaemic stroke and coronary artery disease were also received for drug XYZ. A thorough search of the literature was done and it was found that the study drug XYZ could inhibit an important biological molecule; this action could mechanistically explain the serious side-effects that had occurred.

After analysing the ADRs in detail, the TA-ADR came to a conclusion that though the co-morbid conditions of the patients could have contributed to these events, considering the long half-life (21 days) of drug XYZ and the protective role of the important biological molecule (which is blocked by drug XYZ), the possible role of the suspect drug could not be excluded. The TA-ADR observed that the use of drug XYZ could result in serious side-effects. The PI of the study was informed

about this concern. The TA-ADRs informed the IRB during its full board meeting about the danger of continuing the study drug. After a thorough discussion, the IRB members came to the conclusion that safety of the patients participating in the particular study was at risk. All the members agreed on this point and this decision was minuted by the IRB. The minutes were sent to all the IRB members for their final approval and it was decided by the IRB to withhold the study. In May 2010, the IHEC decided to withhold the study till the safety of the drug XYZ was fully established. The PI, on the invitation of the IHEC, explained the matter before the full board review meeting of the IHEC. A few weeks later, in June 2010, the PI approached the principal of the institution with a letter from the sponsor of the trial with an accompanying communication from the United States Food and Drug Administration (US FDA) to put the trial on hold, which corroborated the IHEC's decision to withhold the study.

This experience with an exclusive TA-ADR underlines the need for the same. We have now decided to strengthen the office of the TA-ADR by introducing more innovations such as assigning a colour code to the sheets in which ADRs are printed, based on the seriousness criteria.

Other lessons learned include: (i) The importance of conducting periodic reviews by the IHEC to identify areas of strength and weakness, ways and means to strengthen the system further, as also to strengthen the SOP; and (ii) assign specific roles for each of the members, eg, we have designated one member of the IHEC as "Member in charge of protocol amendments" (this system has since been replaced with that of the "Primary reviewer" of each protocol prospectively following it (all aspects including amendments) up until the closure of the study) and another member as "Member in charge of stored tissues".

We report this with a view to share this experience with others.

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