A SENTINEL EVENT BASED ADVERSE EVENT MONITORING SCHEME

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The results reported here are the FDA author's views and do not represent FDA policy.

Abstract

Monitoring for adverse events is mandatory in many clinical trials. The protocol may account for events that are anticipated because of prior experience with the drug under study or with drugs in the same class. For these events, the purpose of monitoring may be to obtain an accurate estimate of the incidence rates.

Monitoring for unanticipated, spontaneous, or idiosyncratic events is more challenging. Data Safety Monitoring Committees (DSMC) often use an informal “sentinel event” method for monitoring unanticipated adverse events of clinical significance. The DSMC might monitor an unexpected death deemed to be potentially related to the product, but it would be unlikely to monitor a relatively minor event like a rash that clears spontaneously without causing systemic effects. We suggest an approach to formalizing this procedure.

If the event is a reaction in one patient (e.g., an unexpected death), a single sentinel event would trigger a monitoring rule. Subsequent monitoring for extremely rare events might use the exponential distribution and determine the time to the kth event which will have the form of a χ² distribution with 2k degrees of freedom. Comparing a treatment with a control group would involve the ratio of two sums and would lead to an F distribution.

If the event is an elevated rate (e.g., a mortality rate due to MI greater than a worrisome level), a set of events would define the sentinel. The triggering level would depend on the product, the type of event, and the rate in the control group. A group sequential testing plan could compare rates at appropriate time intervals.
Some issues include a) how might the DSMC decide to follow a particular event? b) Should monitoring include a formal testing procedure? c) Should the examination be conducted at fixed times or when an event occurs?