Indian Society for Clinical Research

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A Guide to Adverse Events and Serious Adverse Events in Clinical Trials

Issued as an Information Series on Behalf of ISCR

There is often confusion in the understanding of Adverse Events (AEs) and Serious Adverse Events (SAEs) that are reported in the course of a clinical trial. An AE or SAE **in** a clinical trial is often confused as an AE or an SAE **due** to a clinical trial. This leads to misleading conclusions that many people are falling ill or dying due to a clinical trial.

This note on behalf of the Indian Society of Clinical Research, an association of clinical research professionals, aims to create awareness and understanding of Adverse Events and Serious Adverse Events and their occurrence in clinical trials.

We believe that the media can play an important role in educating the larger public about clinical research and addressing misconceptions, while also highlighting the rights and responsibilities of patients. It is only through clinical research that better and more effective treatments can be discovered for lifestyle illnesses and illnesses that are endemic to our country.

a) What is a Serious Adverse Event?

Indian GCP (Good Clinical Practice) Guidelines define an **Adverse Event (AE)** as "any untoward medical occurrence (including a symptom/disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given".

A **Serious Adverse Event (SAE)** is defined as "an AE that is associated with death, inpatient hospitalisation (in case the study was being conducted on out-patients), prolongation of hospitalisation (in case the study was being conducted on inpatients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening".

The international ICH GCP Guidelines are also similar in their description of an AE and SAE.

b) What causes an AE or an SAE in a clinical trial?

There are several factors that can cause an adverse event during a clinical trial including the patient's underlying disease and other pre-existing conditions, age, genetic and environmental factors. It is important to note that Indian GCP guidelines require all SAEs of patients in a clinical trial to be reported, whether related to the trial medication or not.

c) Why do patients in a clinical trial die?

Patients who participate in a clinical trial already have an underlying disease which could be mild, like conjunctivitis or skin ailments, or serious like cancer or a heart condition. The death of a patient in a clinical trial could be due to various reasons, including a natural progression of the disease he or she is suffering from, a new illness he or she may develop, age related disorders, or a complication totally unrelated like an accident.

Most patients who die in a clinical trial do so because of causes unrelated to the medicine being tested. In some studies like oncology studies, death is the end point of the study and such deaths would be reported as death of a patient in a clinical trial. Therefore it is wrong to assume that deaths of all patients in a clinical trial are due to the clinical trial.

In reality, patients who participate in a clinical trial receive a greater degree of medical care and attention than they would under regular treatment because of the high level of investigation and patient management that a clinical study protocol requires.

d) Is there a difference between AEs or SAEs <u>in</u> a clinical trial and AEs or SAEs <u>due</u> to a clinical trial?

Yes there is a big difference. Indian GCP guidelines mandate that all AEs and SAEs must be reported whether study related or not. This could include any AE or SAE like an unrelated serious illness a patient may develop, a fall or an accident at home, an age-related disorder or even death as a natural progression of a disease like cancer. Such events could happen to a patient in a clinical trial but may not be due to the study medication and must still be reported. Therefore it would be wrong to conclude that all AEs or SAEs in a clinical trial are due to a clinical trial. This distinction must be understood and made.

<u>For instance, if a patient in a clinical trial trips and falls in his house and fractures his leg or if he meets with an accident on his way to work or requires an unrelated surgery and any of these require hospitalisation, they have to be reported as an SAE to the regulatory body even though they have no connection with the clinical trial.</u> Therefore all SAEs reported of patients in clinical trials are not necessarily study-drug related.

Causality to the study medication and/or a study related procedure must be established to determine that an AE or SAE is due to a clinical trial.

e) How is causality of an adverse event determined?

As per the guidelines, the investigator in a trial is required to provide a full and thorough causality assessment to the sponsor for each SAE of the clinical trial. In cases where there is a serious unexpected event, the sponsor reviews the assessment by the investigator and in the event the sponsor determines that there is a possible correlation between the SAE and the clinical trial, the sponsor will submit an investigational new drug safety report to the regulators. The causality assessment made by the investigator and the sponsor is reviewed by the Expert Committee and the DCGI who take a final decision on causality.

f) When and how is compensation paid?

There are clear cut procedures laid down for compensation in case of a related SAE as per Indian guidelines.

The Drugs and Cosmetics Rules have been amended vide GSR 53(E) dated 30-01- 2013 inserting a Rule 122DAB and a new Appendix-XII in Schedule Y. The amendment specifies the procedure for processing of reports of SAEs, including deaths, occurring during clinical trials to arrive at the cause of death/injury to the subject, and to determine the quantum of compensation, if any, to be paid by the sponsor or his representative in a time bound manner. In line with the provisions of the amendment, the DCGI determines the quantum of compensation to be paid out based on the recommendations of the Independent Expert Committee. The DCGI has to pass an order as deemed necessary within three months of receiving the report on the fatal Serious Adverse Event. In cases of clinical trial related injury or death, the Sponsor or his representative shall pay the compensation as per the order of the DCGI within 30 days of the receipt of such an order. A provisionally final formula to determine the quantum of compensation has also been developed by the Independent Expert Committee.

g) How are SAEs recorded and reported?

Schedule Y of the Drugs and Cosmetics Act stipulates that "any **unexpected serious adverse event** (SAE) (as defined in GCP Guidelines) occurring during a clinical trial should be communicated promptly (within 14 calendar days) by the Sponsor to the Licensing Authority and to the other Investigator(s) participating in the study**."**

Reporting of an SAE begins immediately after a patient signs an Informed Consent Form and even before the first dose of a trial drug is administered.

While reporting of SAEs is done in compliance with regulatory guidelines, it must be highlighted that all unexpected SAEs are mandatorily reported, whether they are study related or not.

h) How different are SAE reporting procedures in India compared to other countries?

There is a marked difference in reporting procedures for SAEs in India as compared to other parts of the globe. In India, any **Unexpected Serious Adverse Event** in a clinical trial patient has to be reported, whether study related or not, whereas in most countries overseas, it is only **Suspected, Unexpected Serious Adverse Drug Reactions** that are reported.

An Adverse Drug Reaction is one where there appears to be a reasonable possibility that the adverse event is related with the medicinal product being studied.

This in itself accounts for the number of SAEs reported in India being high although again, we would like to stress that this does not mean that all the SAEs are study related.

About ISCR

The **Indian Society for Clinical Research (ISCR)** (www.iscr.org) is an association of clinical research professionals which aims to build awareness of clinical research as a specialty in India and to facilitate its growth in the country while helping to evolve the highest standards of quality and ethics. Therefore awareness and education are a key focus and objective for us.

In the larger context of India's requirements and the growing incidence of endemic diseases and emerging lifestyle diseases, clinical research is needed to develop new and effective medicines and vaccines to tackle our mammoth disease burden. India has 16% of the world's population and 20% of the global disease burden and yet, less than 1.5% of global trials take place in India. It is only through clinical research that we will be able to find newer and better medicines to treat our population and reduce mortality rates for various diseases, including those unique to our part of the world.

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