SAFETY REPORTING :
Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO) and Serious Adverse Events (SAE)

What is "Unanticipated Problems Involving Risk to Subjects or Others" (UPIRTSO)?

UPIRTSO is an event that fulfills the following three criteria:

a) **Unexpected**
The nature, severity and frequency are not consistent with the research procedures described in protocol-related documents or the characteristics of the subject population.

b) **Related, or Possibly Related to participation in research**
There is a possibility that the incidence, experience or outcome may have been caused by the research procedures.

c) **Suggests that the research places participants or others at a greater risk or harm.**

Note:

An event which fulfils the first two criteria of **Unexpectedness and Relatedness** will be reportable to **NHG DSRB** for further review. An UPIRTSO **need not be SERIOUS** (as in death, life-threatening, or resulting in hospitalization) to be reportable.

What is a Serious Adverse Event (SAE)?

Adverse Event: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

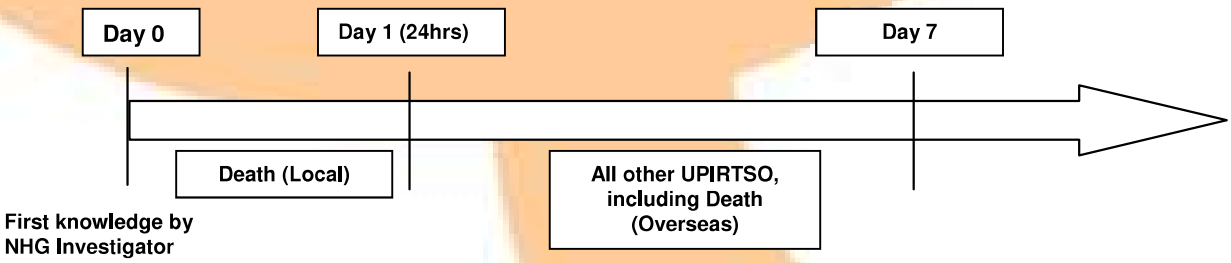
Serious Adverse Event: any untoward medical occurrence that at any dose results in

- death
- is life-threatening
- requires inpatient hospitalization or prolongs existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- or requires medical or surgical interventions to prevent any of the above outcomes.

Note:

An SAE need NOT be UNEXPECTED or RELATED to the medicinal product to be reportable to the **Sponsor and Health Sciences Authority (HSA).**

What are the Reporting Timelines for UPIRTSO (to DSRB)?



Note:

For local (occurring in NHG, NUHS, AH sites) reports of death, regardless of expectedness or relatedness, they must be reported to DSRB within 24 hours.

For overseas reports of death, these are to be reported as per UPIRTSO guidelines, i.e. only cases which are unexpected and related need to be reported as per UPIRTSO guidelines, i.e. only cases which are unexpected and related need to be reported, following the 7 day timeline.

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A) UPIRTSO: ✓ **SAE:** ✗

Breach in Data Confidentiality

An investigator conducting behavioral research collects individually identifiable sensitive information about depression and mental health status by surveying university students

The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work.

Incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data.

Non-Fatal Drug Dosing Error

As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation.

Incident was (a) unexpected; (b) related to participation in the research; and (c) placed subject at a greater risk of physical harm.

B) UPIRTSO: ✗ **SAE:** ✓

Known Incidence of Adverse Events

A subject participating in a phase 3, clinical trial comparing the relative safety and efficacy of a new chemotherapy agent combined with the current standard chemotherapy regimen, versus placebo combined with the current standard chemotherapy regimen, for the management of multiple myeloma develops neutropenia and sepsis. The subject subsequently develops multi-organ failure and dies.

Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections is a known complication of the chemotherapy regimens being tested in this clinical trial and these risks are described in the IRB-approved protocol and informed consent document. The investigators conclude that the subject's infection and death are directly related to the research interventions. A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection, and death are within the expected frequency.

Adverse Event Arising from Underlying Condition and Not Related to Study

A subject with advanced renal cell carcinoma is enrolled in a study evaluating the effects of hypnosis for the management of chronic pain in cancer patients. During the subject's initial hypnosis session in the pain clinic, the subject suddenly develops acute chest pain and shortness of breath, followed by loss of consciousness. The subject suffers a cardiac arrest and dies. An autopsy reveals that the patient died from a massive pulmonary embolus, presumed related to the underlying renal cell carcinoma. The investigator concludes that the subject's death is unrelated to participation in the research. This example is not an unanticipated problem because the subject's pulmonary embolus and death were attributed to causes other than the research interventions.

Where Can I Get More Information?

Investigator Manual Chapter 04 Submissions to DSRB (UPIRTSO)

PCR SOP 501-C05 UPIRTSO

OHRP Guidance on Reviewing and Reporting UPIRTSO and Adverse Events
http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm