Office of Research Integrity

According to the Food & Drug Administration (FDA) and the Office for Human Research Protections (OHRP), the vast majority of adverse events in human subjects are not Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs). Prompt Internal UPIRSO Reports are reviewed at the next available meeting by the convened IRB. This level of attention should be reserved for events that meet either all of the three criteria below or other categories in the UK IRB Policy on Unanticipated Problem and Safety Reporting.

This document was developed to help research teams understand the differences between an internal prompt event and an internal non-prompt event, based on the first three prompt reporting criteria in the UK UP Policy. Note: the policy includes other categories such as research related death and other events that warrant prompt reporting based on the Principal Investigator's judgement. However, this guidance addresses the first three criteria to clarify when they are likely and are not likely met.

An internal prompt event = UPIRSO. This type of event must meet **ALL 3** of the criteria below . If the study team considers the event to meet **ALL 3** criteria, the internal prompt form should be filled out and submitted in the EIRB. **Once an internal prompt is submitted, the event is automatically placed on the next available convened meeting.**

A non-prompt event does NOT meet the criteria for the UPIRSO. Can a non-prompt meet some, but not all 3 of the criteria? **YES, it can.** For example, a subject can state to the study team they have a sinus infection (unexpected) but is enrolled in an exercise study (not related to the sinus infection).

Table One: UPIRSO – first three key criteria for consideration

INTERNAL EVENTS or PROBLEMS	CONSIDERATIONS OF EVENTS
1. Unexpected (in terms of nature, severity, or frequency), **AND**	Not described or more severe or frequent Not described in investigational plan or Investigator Brochure, or more severe or frequent than what is described.
2. Related or possibly related, **AND**	Evidence to suggest a causal relationship
3. Suggests that the research places subjects or others at a greater risk of harm.	The event put subjects at a potential greater risk of harm versus what was previously discussed in the consent form they signed. *For FDA-regulated, may include serious adverse event (SAE) or unanticipated adverse device effect (UADE)*

(IF ALL THREE ABOVE CRITERIA ARE MET, THE EVENT = UPIRSO)

The following are examples to help illustrate application of the UPIRSO criteria. For Investigator-Initiated FDA Clinical Investigations, also refer to the FDA reporting requirements for studies conducted with an Investigation New Drug (IND) or Investigational Device Exemption (IDE).

Clearly, sponsor mandates, extenuating circumstances, or additional information could alter an investigators decision to submit a prompt report. However, the goal, is for the convened IRB to focus on events that are critical, interpretable, and have potential to alter the risk-benefit ratio of the research. Non-prompt events may still be reported in aggregate or summarized at continuing or annual review, along with the investigator's overall safety assessment. Note: This guidance relates only to UK IRB reporting. Investigators are still responsible for providing subject care and resources for all research related events.

Table 2: Scenarios or examples that are likely not a UPIRSO

Likely not a UPIRSO
Low white blood cell count and anemia in a subject participating in a chemotherapy study **(expected)**
Subject in a study testing a leg brace is diagnosed with COVID-19 **(unrelated)**
Subject has an abnormal lab test result, but elevation is within protocol expectations of up to one-time upper limit of normal **(expected)**
Subject in a medical device study is critically injured as a passenger in a car collision **(unrelated)**
Male subject in neurocognitive study diagnosed and treated at an emergency department with inflamed prostate. There is no known relationship with the drug and the subject meets the demographic profile for which this condition commonly occurs. **(unrelated)**
In a behavioral study on seasonal depression, a subject answers an interview question indicating they have considered self-harm. A subject answering questions regarding self-harm is expected and is one of the study end-points being assessed. However, the study protocol includes safeguards including a warm hand-off to a mental health professional and follow-up support. **(expected)**

Table 3: Scenarios or examples that appear to meet all three criteria as a UPIRSO

Likely a UPIRSO:
Subject in a Phase II investigational drug study is hospitalized and diagnosed with acute hepatic injury. The subject has no underlying liver disease and reports no injury or other extenuating circumstances. The investigator brochure does not report prior instances of liver injury; however, mildly elevated liver enzymes was found in 2% of phase I participants. *This scenario illustrates a serious event not previously identified in severity in the previous research or investigational plan. The absence of an underlying condition and related mild events suggest a possible causal relationship.*
Study drug dispensing error that resulted in subject receiving but not taking the wrong dosage of study drug. *While harm did not occur in this scenario, drug errors hold potential for new risks to subjects. The event warrants a root-cause analysis and perhaps corrective action to ensure proper dosing.*
During a Phase IV post-approval drug study, FDA issues a black box warning for the marketed product. *The warning clearly meets the related criteria, and the severity of the event is unexpected and holds potential for harm to subjects or others. A black box warning is the highest level warning communicated by the FDA.*
Subject with no known allergies is treated for an unexpected allergic response warranting urgent care. The subject is a participant in a clinical trial. Upon inquiring, the sponsor's medical monitor cannot rule out association with study drug. *Seeking guidance from a sponsor's medical monitor may help solidify information or fill in gaps that could signify a possible trend.*
A flash drive containing identifiable research data is stolen from the study team. Information includes responses to surveys on engagement in questionable business practices. *The scenario adds new unanticipated risks that are related to research and present the potential for harm to subjects/others*

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