IRB Member Review of Reported Events as Possible Unanticipated Problems

When the IRB is asked to determine if a reported event is an unanticipated problem (UP), the Board needs to decide if **ALL** 3 criteria are met. The event (*in summary*) must:

1. Be **unexpected** AND
2. Be **related or possibly related** to the research AND
3. **Places participants or others at a greater risk of harm** than was previously known or expected

Criterion	IRB considerations based on complete criteria description
Is the event unexpected?	Is the event unexpected in **nature**, **severity**, or **frequency*** given the following? (a) the research procedures described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied
Is the event related or possibly related to the research?	Is the event at least possibly related to the research procedures or interventions? *Possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.
Does the event place participants or others at a greater risk of harm than was previously known or expected?	*Others* may include research staff, family members or other individuals not directly participating in the research. While the event may have caused harm, it is enough to have caused a greater *risk of harm* to meet this criterion. *Harm* is not limited to physical harm, but can also mean psychological, economic or social harm.

Additional IRB responsibilities: When the IRB determines an event is a UP, IRB members should consider:

- Are corrective actions that are planned or already taken by the investigator appropriate and sufficient?
- Are risks to participants or others still minimized and reasonable in relation to anticipated benefits?
- Are changes to the protocol and/or consent needed? (e.g., Should safety monitoring frequency be increased? Does the consent need to be updated to notify subjects of the new risk? Should existing subjects be reconsented?)
- Are risks to participants such that IRB should consider suspending enrollment? Suspend/terminate entire study?

How does reporting of adverse events to the IRB relate to reporting UPs ?

- Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on protocols overseen by the NIH IRB *only* need to be reported to the NIH IRB in an expedited manner if they meet criteria for an unanticipated problem**.**
- If these AEs and SAEs are not UPs, they do not require expedited reporting to the NIH IRB and should be submitted at the time of Continuing Review as part of a high-level summary.

What happens when a UP occurs on a protocol not overseen by the NIH IRB, but it could affect subjects on a protocol for which the NIH IRB is the IRB of Record?

NIH PIs may receive an IND Safety Report about an event on a study **not under NIH IRB** but that uses the same investigational agent being used in their NIH study. The NIH PI must evaluate the Safety Report and determine if the event is a possible UP or new information that might affect the willingness of subjects on the NIH study to enroll or remain in the study. If so, the event should be reported in the eIRB system as new information. The NIH IRB will not make the UP determination since they are not the IRB of Record for the study on which the event occurred. However, the NIH IRB reviews the related proposed amendment to the NIH protocol/consent based on the reported event.

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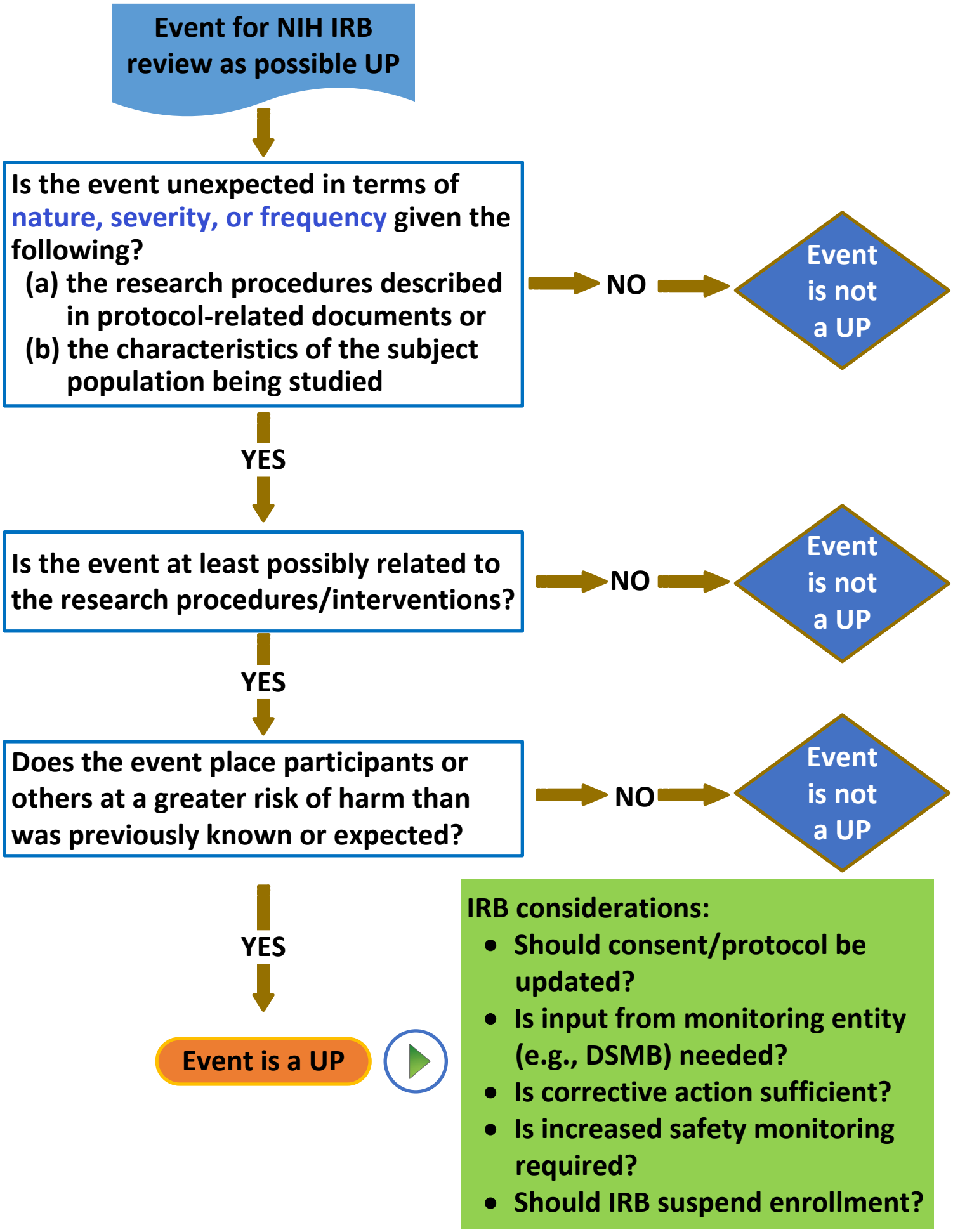
*For example:

- Unexpected **nature**: Participant experiences unexplained severe bleeding while receiving the study agent in an early phase trial, and neither the protocol, consent nor the IB list bleeding as a possible risk
- Unexpected **severity**: Participant experiences liver failure while taking oral study agent while the IB, protocol and consent list risk of only mild reversible elevation in LFTs
- Unexpected **frequency:** IB and protocol list a 10% risk of possible mild rash requiring topical steroids but at CR, PI notes 25% of participants had such a rash while receiving the study agent

References: NIH Policy 3014-801, *Reporting Research Events.*
OHRP Video *Reporting to OHRP: Unanticipated Problems*
OHRP Guidance: *Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events* (2007)


Event for NIH IRB review as possible UP
Is the event unexpected in terms of nature, severity, or frequency given the following?
(a) the research procedures described in protocol-related documents or
(b) the characteristics of the subject population being studied
NO
Event is not a UP
YES
Is the event at least possibly related to the research procedures/interventions?
NO
Event is not a UP
YES
Does the event place participants or others at a greater risk of harm than was previously known or expected?
NO
Event is not a UP
YES
Event is a UP
IRB considerations:
Should consent/protocol be updated?
Is input from monitoring entity (e.g., DSMB) needed?
Is corrective action sufficient?
Is increased safety monitoring required?
Should IRB suspend enrollment?