NIH IRB & Research Compliance Review Committee (RCRC) Review of Research Related Events

Purpose: This reference guide supports NIH IRB and RCRC members in evaluating reportable research events, clarifying committee responsibilities, and determining whether an event meets the definition of an Unanticipated Problem (UP).

NIH Roles and Responsibilities

NIH IRB	NIH RCRC
Reviews potential unanticipated problems and significant new information.	Reviews potential serious and/or continuing noncompliance when NIH is the Reviewing IRB.
Determines whether reported events meet the criteria for an Unanticipated Problem.	Makes final determinations regarding serious and/or continuing noncompliance.
May require protocol/consent revisions, suspend enrollment, or terminate approval.	May require corrective actions and suspend or terminate research approval.

When the IRB is asked to determine if a reported event is a UP, the Board needs to decide if **ALL** 3 criteria are met.
The event must:

1. **Unexpected:** The event is unexpected in nature, severity, or frequency. AND
2. **Related or Possibly Related**: There is a reasonable possibility that the event resulted from research procedures or interventions. AND
3. **Greater Risk:** The event places participants or others at greater risk of harm than previously known or anticipated.

Criterion	IRB considerations based on complete criteria description
Is the event unexpected?	Is the event unexpected in **nature**, **severity**, or **frequency** [1] given the following: (a) the research procedures described in the protocol-related documents (e.g., IRB-approved protocol and informed consent document); and (b) the characteristics of the population being studied.
Is the event related or possibly related to the research?	Is the event at least possibly related to the research? (Is there is a reasonable possibility that the event 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?	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. It can also mean psychological, economic or social harm. *Others* may include research staff, family members or other individuals not participating in the research.

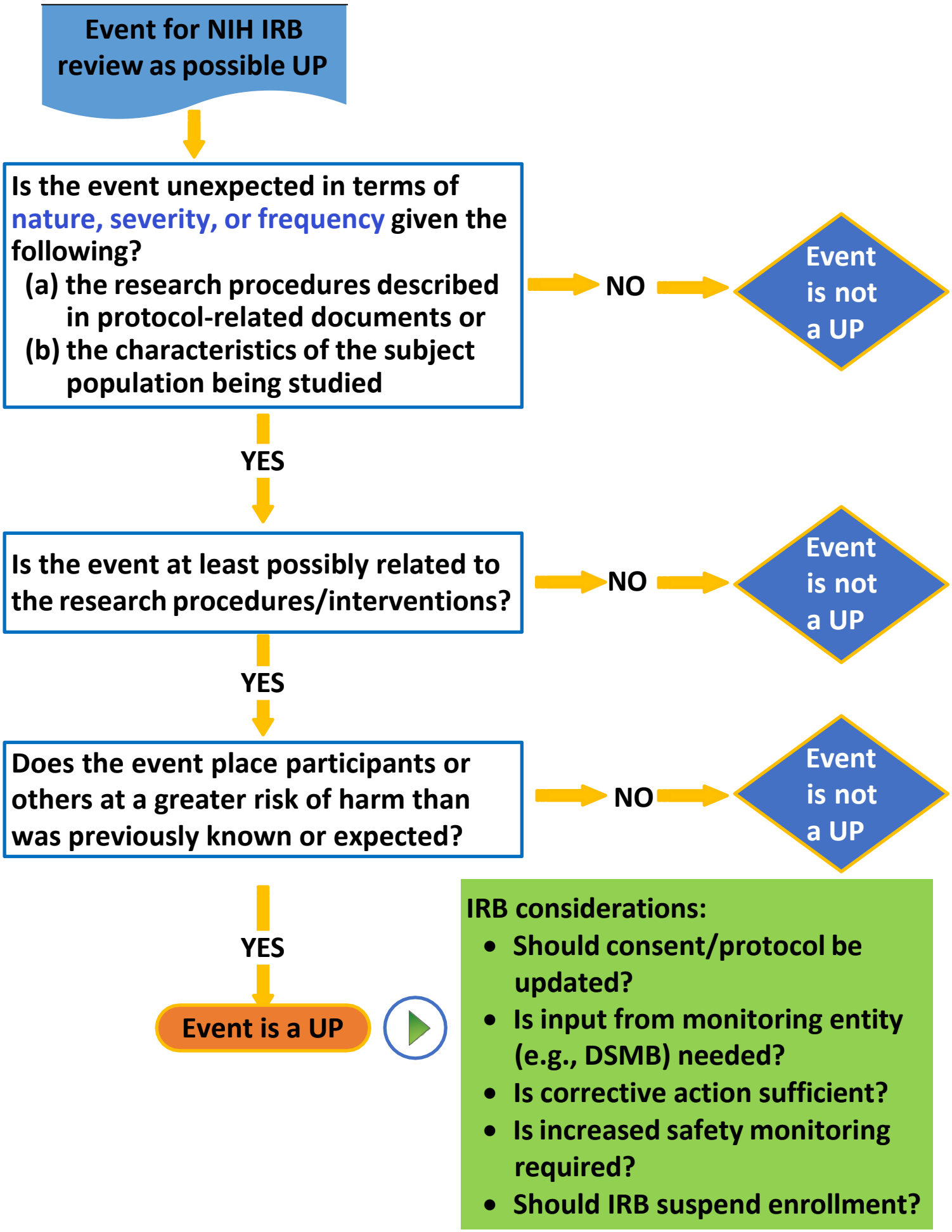
Additional IRB responsibilities: When the IRB determines an event is a UP, IRB members should consider:

- 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 such that IRB should consider suspending enrollment? Should the IRB suspend/terminate entire study?

[1] For example:

- Unexpected **nature**: Participant experiences unexplained severe bleeding while receiving the study agent in an early phase trial. Neither the protocol, consent nor the IB list bleeding as a possible risk.
- Unexpected **severity**: Participant experiences liver failure while taking oral study agent. 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* and Policy 3014-802, *Non-Compliance in Human Subjects Research*


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?