This guidance applies to Stanford University human subject research and details events or circumstances that must be ***promptly*** reported to the IRB during the conduct of human subject research. (Human subject research performed with veterans at the VAPACHS follows different definitions and timelines, see Resources below). "Prompt reporting" is done using the Report Form in eProtocol.

Events and information which require prompt reporting to the IRB

1) Unanticipated Problems Involving Risks to Participants or Others (UPs)

Events (internal or external, deaths, life-threatening experiences, injuries, or other) occurring during the research study, which in the opinion of the Monitoring Entity or the PD meet ***all*** of the following criteria:

a) Unexpected
in terms of nature, severity, or frequency, given (a) the research procedures described in the protocol-related documents such as the IRB-approved research protocol and informed consent document or the Investigator's Brochure, and (b) the characteristics of the subject population being studied;
AND

b) Related or Possibly Related to participation in the research or there is a reasonable possibility or likelihood
that the incident, experience, or outcome may have been caused by the procedures involved in the research;
AND

c) Places Subjects or Others at a Greater Risk of Harm
the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm, including harm related to breaches of privacy) than was previously known or recognized.

NOTE:

- *A "UP" generally will warrant consideration of substantive changes in the research protocol or informed consent process/document, or other corrective actions, in order to protect the safety, welfare, or rights of subjects or others.*

2) New Information that indicates a change to the risks or potential benefits of the research in terms of severity or frequency or impacts the subject's willingness to participate (e.g., DSMB/DSMC Report, other safety information or publication, suspension or premature termination by the sponsor or investigator).

3) Noncompliance: An action, inaction, or activity, whether by the investigator, study staff, or others involved in human subject research, that is at variance with the approved IRB protocol, other requirements and determinations of the IRB, the HRPP Policy Manual and other applicable policies of Stanford University, SHC, LPCH, VAPAHCS (e.g., VHA Handbook 1200.5), Palo Alto Veterans Institute for Research (PAVIR) or relevant state or federal laws. The following are always considered noncompliance: human subjects research conducted without IRB approval, or approved by an outside IRB, without prior notice to Stanford's IRB (or Stanford IRB approval, if required under Stanford policies); or change(s) to the research implemented without IRB approval except when necessary to eliminate apparent immediate hazards to the subject.

When the event is:

- ***Possibly serious***: Any behavior, action, inaction, or omission in the conduct or oversight of human research that, in the judgment of the IRB, has been determined to:

•adversely affect or compromise the rights or welfare of participants;
•harm or materially increase exposure to significant risk of harm to a research participant(the IRB does not have to find that harm has occurred, or was likely to occur, to make a determination of serious noncompliance);
•result in a detrimental change to a participant's clinical or emotional condition or status; or
•compromise the integrity or validity of the research.

- ***Possibly continuing***: A pattern of repeated instances of noncompliance that:
  - Continues to occur after discovery of noncompliance or implementation of a preventive action plan; or
  - Results from failure to implement a preventive action plan approved by the IRB; or
  - A circumstance in which an investigator or other study staff fails to cooperate with investigating or correcting non-compliance.

4) **Complaint** unresolved by the research team

5) **Incarceration** when in the opinion of the PD it is in the best interest of the participant to remain on the study.

6) **Unanticipated adverse device effect (UADE)**
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. 21 CFR 812.3(s)
More guidance on UADE

7) **Other events or information**
Examples include: a deviation intended to eliminate an immediate hazard to a participant, suicide or suicide attempt of a participant, other Audit or Monitoring Visit reports and Corrective Action Preventative Action (CAPA) plans. Report only after consulting with the IRB Panel Manager.

How to Submit a Report; Timeframes

➢ **Submit to IRB** using eProtocol Report Form (https://eprotocol.stanford.edu/irb)

- **Timeframe for UP reports depends on Monitoring Entity*** (for DOE research see Other Federal Agencies - Additional Requirements [GUI-42]

  - ***If PD is the only monitoring entity***
    Items 1 - 6 should be reported ***directly*** to the IRB ***within 10 working days*** from when the PD learns of the event or new information.

  - ***If there is a monitoring entity in addition to, or other than, the PD***
    Report to the IRB using this form ***within 10 working days*** from receiving assessment from monitoring entity. The PD should report to the IRB when the event has been assessed by the monitoring entity to be a UP.

- **Timeframe for Reportable Information (items 2 - 7)**
These should always be reported by the PD ***directly*** to the IRB ***within 10 working days*** from when the PD learns of the event or new information.

- **Unexpected deaths or life-threatening experiences** related to the research (at Stanford, or when STANFORD is the coordinating institution in a multi-site study) must be reported to the IRB ***within 5 working days*** from PD learning of event.

Definitions

1. ***Protocol-related documents*** refer to the IRB-approved research protocol, informed consent document, investigator brochure, protocol, package insert, or label.
2. ***Characteristics of the subject population being studied*** refers to the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.
3. **Related to participation in the research** - In general if event is determined to be caused at least partially by the procedures involved in the research it would be considered *related* to participation in the research; if caused solely by an underlying disease, disorder, or condition of the subject, or other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject it would be considered *unrelated* to participation in the research.
4. ***Adverse events*** need not be "serious" to qualify as "harmful". However, "serious adverse events" always meet the "Harmful" criterion.
5. ***Serious adverse event*** only needs to be reported promptly if it is *also* a UP. An SAE is defined by OHRP as an event that:
   - results in death;
   - is life-threatening (places the subject at immediate risk of death from the event as it occurred);
   - results in inpatient hospitalization or prolongation of existing hospitalization;
   - results in a persistent or significant disability/incapacity;
   - results in a congenital anomaly/birth defect; or
   - based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition
5. ***Other events that might also be UPs:*** events (that are not serious by FDA definition) could also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical, psychological, economic, or social harm than was previously known or recognized, e.g. a privacy breach.
6. ***FDA-regulated drug studies:*** *See definitions in FDA regulations at 21 CFR 312.32(a).*

Resources: Regulations and Guidance	
OHRP	• 45 CFR 46.108 (a)(4) • *Reviewing and Reporting UPs Involving Risks to Subjects or Others and Adverse Events* - Guidance
FDA	• 21CFR 812.150 Investigational Device – reports • 21 CFR 312.32(a) Investigational New Drug – safety reports • Adverse Event Reporting to IRBs - Improving Human Subject Protection – Guidance • Safety Reporting Requirements for INDs and BA/BE Studies – Guidance • Safety Reporting Requirements for INDs and BA/BE Studies – Small Entity Compliance Guide
VA	• VHA Directive 1058.01

Resources: Other References	
Stanford HRPP	• Ch 3.10 Unanticipated Problems Involving Risks to Participants or Others (UPs), and Other Reportable Information • Other Federal Agencies - Additional Requirements [GUI-42] • Reviewing Veterans Affairs (VA) Research [AID-27m] • Unanticipated Adverse Device Effect (UADE) [GUI-P14]