Trustees of Dartmouth College
COMMITIEE FOR THE PROTECTION OF HUMAN SUBJECTS
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Reporting of Unanticipated Problems, Serious Adverse Events, and Unanticipated Adverse Device Effects to the Committee for the Protection of Human Subjects at Dartmouth College

Scope and Rationale:
This policy defines the reporting requirements for Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) and applies to all research approved by Dartmouth College CPHS for which The CPHS serves as the IRB of record, or research deemed by the CPHS to qualify for exemption. The rationale for reporting Unanticipated Problems Involving Risks to Subjects or Others (UPRs) to the CPHS is to ensure that the research team and the CPHS fulfill their obligations to protect human research subjects. Federal regulations require Dartmouth College to have written procedures for ensuring that Unanticipated Problems Involving Risks to Subjects or Others (UPRs) are promptly reported to the CPHS, appropriate institutional officials, and federal agencies. See 45 CFR §46.103(b)(5), 21 CFR §56.108(b)(1)

Statement
The following information describes the position of the CPHS on the reporting of unanticipated problems involving risks to subjects or others. The CPHS position applies to the reporting of certain serious adverse events **(SAE),** Unanticipated Problems Involving Subjects or Others **(UPR),** investigational new drug **(IND)** safety reports, as well as unanticipated adverse device effects **(UADE).**

Unanticipated problems can occur in any type of research (medical or non-medical) and may include occurrences such as serious adverse events, subject complaints, protocol deviations, and other untoward events involving risk. Events requiring prompt reporting by investigators and research staff may involve physical, psychological, social, legal, or economic harms. Additionally, a UPR may expose participants to potential risk, but does not involve direct harm to participants. The Principal Investigator (PI) must make any changes to the protocol, informed consent documents, recruitment materials, and/or other documentation that the PI deems is necessary and as may be required by the IRB in connection with such reports.

The position taken by the CPHS on adverse event reporting does not eliminate any requirement for an investigator to report adverse events to the FDA, other regulatory or funding agencies, or the sponsor. It also does not alter the requirement for the principal investigator to review adverse event reports s/he receives from the sponsor or other agency.

The CPHS should be promptly notified of unanticipated problems involving risks to subjects participating in research, or others who are affected by the research. Reporting includes only certain events or problems. Reporting criteria differs based on whether the occurrence was internal or external.

Definitions:

Unanticipated Problem Involving Risks to Subjects or Others (UPRs) Any incident, experience or outcome that meets ALL 3 of the following criteria:

1.Is **unexpected** (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND

2. Is **related or possibly related** to participation in the research (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); AND

3**. Suggests that the research places subjects or others at greater risk of harm** (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPRs) may be medical or non-medical in nature, and include – but are not limited to – serious, unexpected, and related adverse events and unanticipated adverse device effects (see below). Please note that adverse events (as defined below) are reportable to the IRB as UPRs only if they meet all 3 criteria listed above.

Adverse Event: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

Serious: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect.

Unexpected: Any adverse drug experience, the specificity, severity or frequency of which is not consistent with the current investigator brochure or consent form.

Related: A reasonable possibility exists that the experience may have been associated with the procedures involved in the research.

Unanticipated adverse device effect: Any serious adverse effect on health or safety, or any life-threatening problem or death, caused by or associated with an investigational device.

Internal events involves a Dartmouth site or another CPHS-reviewed site or a Dartmouth research participant (regardless of location of the participant at the time of event).

External events are those that occur at a non-CPHS reviewed site and with participants that are not research participants under CPHS oversight. This also refers to important new information that goes beyond discrete, individual events, such as new animal data, or a black box warning.

Prompt Reporting: The appropriate time frame for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted. For example, an unanticipated problem that resulted in a subject's death or was potentially life-threatening generally should be reported to the IRB within a shorter time frame than other unanticipated problems that were not life-threatening. Therefore, please adhere to the following guidelines in order to satisfy the requirement for prompt reporting:

1. Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.
2. Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

CPHS Review of Reports

The CPHS reviews each reported adverse event to determine whether or not:

1) The participants in the study should receive additional information related to continuing their participation;
2) The protocol, study plan or consent form should be modified;
3) The study should be temporarily suspended; and
4) What actions, if any, should be taken to protect participants and/or others.

If the CPHS determines that some action in response to the adverse event is necessary, the CPHS will promptly inform the principal investigator.

Incidental findings, as defined below, typically do not qualify as an Unanticipated Problem Involving Risks to Subjects or Others

The CPHS does not review reports for adverse events that occurred before the study was approved by the CPHS. Important safety information discovered prior to the CPHS review should be constituted within the Investigator's Brochure and addendums, Protocol, Consent Form, and other such documents.

Data and Safety Monitoring

Appropriate monitoring of study data is an important safeguard for the human subjects who participate in clinical trials. Data safety monitoring (DSM) requirements depend on the nature, size, and complexity of each clinical trial. The Committee for the Protection of Human Subjects at Dartmouth (CPHS) is not a data safety monitoring committee. Appropriately designed DSM should be described in every CPHS Study Plan. With each request for renewal of CPHS approval, all relevant DSM summary reports should be included with the application materials.

For additional information about adverse event reporting requirements, please consult the FDA regulations on unanticipated adverse device effects at 21 C.P.R. 812.!50 or on IND safety reports at 21 C.F.R. 312.32, as well as the clinical trial agreement with the sponsor.

References:

45 C.F.R. 46.103(b)(5)
21 C.F.R. 312.32

21 C.F.R. 812.3 and 812.150(a)(l)
January 15, 2007 OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
January, 2009 FDA Procedural Guidance for Clinical Investigators, Sponsors, and IREs: Adverse Event Reporting to IREs- Improving Human Subject Protection