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U N I V E R S I T Y

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(Thursday 8:34am) 18 January 2001

Memorandum

To: Center for Clinical Trials faculty and staff

Fr: Curt Meinert

Re: Adverse event reporting good practice policies and procedures (GPPP)

Definitions

adverse drug experience (ADE) *n* - As defined in the Code of Federal Regulations for the **Food and Drug Administration**: *Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose, whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.* (*Code of Federal Regulations*; 21, Parts 300-499, Revised as of April 1, 1994) rt: **safety report**, **serious adverse drug experience**, **unexpected adverse drug experience**

adverse drug reaction (ADR) *n* - A **drug reaction** that results in hospitalization, a prolongation of hospitalization, or that otherwise has **negative** health implications for the **patient** having such a reaction. rt: **toxic drug reaction**, **serious adverse drug experience** ***Usage note***: See **drug reaction**.

adverse event (AE) *n* - 1. Any unfavorable **sign**, **symptom**, state, condition, or laboratory finding in a **study subject**. 2. Any such sign, symptom, state, condition, or laboratory finding, except one considered to be associated with a **beneficial treatment effect**. 3. An **event** seen to threaten the integrity of a **study**. 4. **reportable event** rt: **adverse reaction** ***Usage note***: Not to be used interchangeably with **adverse reaction**. Best reserved for defns 1 and 2. See **reportable event** for additional comments.

adverse reaction *n* - Broadly, a **reaction** that has negative consequences or implications for the one experiencing it and that is the result of some act, agent, or stimulus. In the context of **trials**, such a reaction due to or that is attributed to a **study treatment**; **adverse drug reaction** when the treatment involves a **drug**. ***Usage note***: Not to be used interchangeably with **adverse event**. In the context of trials, adverse reactions represent that subset of adverse events due or attributable to **study treatments**.

adverse side effect *n* - A **side effect** that has adverse health implications for the **patient** having such a side effect. rt: **toxic side effect** ***Usage note***: See **side effect**.

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adverse treatment effect *n* - A **treatment effect** that has **negative** health implications; a **treatment effect** contrary to the one intended or desired. ant: **beneficial treatment effect**

benefit *n* - [ME, fr AF *benfet*, fr L *bene factum*, fr neut of *bene bactus*] Something that promotes well-being or that provides an advantage.

investigational new drug safety report *n* - A report to the **Food and Drug Administration** of an **adverse drug experience** in relation to an **investigational new drug** that is both serious and unexpected; written or telephoned. In relation to such reports, the regulations specify for written reports: *The sponsor shall notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with use of the drug that is both serious and unexpected. Such notification shall be made as soon as possible and in no event later than 10 working days after the sponsor's initial receipt of the information. Each written notification shall bear prominent identification of its contents, ie, "IND Safety Report". Each written notification to FDA shall be transmitted to the FDA division of the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research which has responsibility for review of the IND. In each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports.* In regard to telephone reports, the regulations specify: *The sponsor shall also notify FDA by telephone of any unexpected fatal or life-threatening experience associated with use of the drug in the clinical studies conducted under the IND no later than 3 working days after receipt of the information.* (*Code of Federal Regulations*; 21, Parts 300-499, Revised as of April 1, 1994) syn: IND safety report, **safety report** (defn 2) rt: **serious adverse drug experience**, **unexpected adverse drug experience**

reportable event *n* - 1. **adverse drug experience**, **serious adverse drug experience**, **unexpected adverse drug experience** 2. **adverse event** 3. Any **event** or experience relating to a **study subject** and relevant to an oversight body, such as an **IRB**, in determining whether an approval should be maintained; any such event or occurrence listed as needing to be reported to an oversight body, such as an IRB as a condition for approval or continuing approval. 4. Any event, circumstance, or occurrence threatening the integrity of a **study**. 5. Any event or occurrence listed as reportable by an extant governing, funding, oversight, or regulatory authority, such as the **NIH**, **FDA**, and **ORI**. rt: **reported event** ***Usage note***: Problematic when used in the absence of defining detail regarding what, when, how, and where to report. The domain of reportable events is subject to change depending on perspective. Events considered not reportable during conduct of a study may be seen as reportable when a study is audited or reviewed (see usage note for **reported event**). It is up to **study investigators** to develop and maintain essential reporting procedures in regard to the entire domain of events implied above. The duty to report extends to the broad class of events covered by definition 5, including events of **fraud**, though the guidelines for deciding when the suspicion of fraud is sufficient to trigger a report to one's institutional committee dealing with such matters, or to the ORI are largely

lacking. All **research** involving (see **involve** for usage note) **human beings** is under the purview of IRBs or like named bodies. Approvals from those bodies carry reporting obligations. In all cases, investigators are obliged to report mistakes or misadventures occurring in relation to the processes of **enrolling**, studying, **treating**, or **following study subjects**, and to do so regardless of whether such occurrences were of consequence to persons studied. Generally, approvals are predicated on the presumption that investigators will report deaths and morbidities occurring in the **study population**, that they will do so in a timely fashion, and that they will do so regardless of whether they are considered to be study-related. The presumption, in the case of **multicenter studies**, should be that *study population* is as represented by defn 3 for that term and, therefore, that all investigators and associated IRBs are to receive **reported events** regardless of where first reported. The reporting requirements imposed by the FDA in regard to **safety reports** can lead to a flood of papers in large-scale multicenter trials. IRBs may limit reporting to study-related deaths and morbid events in long-term **treatment trials** where the population being treated has high underlying mortality and morbidity rates. The reporting procedures imposed by the FDA relate to adverse events (defn 1) arising in relation to **drugs**, **biologics**, and **devices** being tested in relation to possible licensure. There are no corresponding procedures for trials of surgical procedures, trials of established medical treatments, or trials of other treatments not under the purview of the FDA. Hence, in those cases, investigators are largely left to establish definitions and procedures for reporting and informing investigators and associated IRBs. The likely minimum reporting requirements (in addition to those concerning mistakes or misadventures as mentioned above) are morbid events or deaths induced or likely caused by a study procedure (including those where it is reasonable to so assume because of temporal relationship); any event occurring in conjunction with a study procedure, administration of a study treatment, or in relation to a change in treatment; deaths or major morbidities occurring in association with initiation or change of treatment; and events or occurrences leading to contact of an IRB by a study subject or representative, and judged by that IRB to have legitimacy.

risk *n* - The **probability** or **chance** of some **event** or condition occurring in a defined time period, especially an adverse event or condition.

risk-benefit ratio *n* - The balance of **benefits** to **risks**; benefits measured against risks. rt: **cost-benefit ratio**

reported event *n* - 1. An **event** reported to a supervising, monitoring, or oversight agency, authority, or body. 2. An **adverse event** (defns 1 and 2) reported to one's **IRB**. rt: **reportable event** ***Usage note***: Ideally, investigators are found to have satisfied their reporting obligations if and when their practices are reviewed. However, the reality is that reporting is the result of judgments that can come into question when a **study** is subjected to searching scrutiny following a high profile event, eg, as in **trials** of fialuridine. See **reportable event** for additional comments.

safety report *n* - 1. **treatment effects monitoring report** 2. A **report** to the **Food and Drug Administration** of an **adverse drug experience** that is both serious and unexpected; written or telephoned; **investigational new drug safety report**; also **IND safety report**.

serious adverse drug experience *n* - 1. An **adverse drug experience** that is **serious**. 2. **Adverse drug reaction** that is **serious**. 3. In FDA parlance, as contained in the Code of Federal Regulations for drugs for that agency: *Any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, a serious adverse drug experience includes any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose. With respect to results obtained from tests in laboratory animals, a serious adverse drug experience includes any experience suggesting a significant risk for human subjects, including any finding of mutagenicity, teratogenicity, or carcinogenicity.* rt: **unexpected adverse drug experience**, **safety report**

unexpected adverse drug experience *n* - An **adverse drug experience** that is **unexpected**. In the parlance of the FDA: *Any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure; or, if an investigator brochure is not required, that is not identified in nature, severity, or frequency in the risk information described in the general investigational plan or elsewhere in the current application, as amended.* rt: **serious adverse drug experience**, **safety report**

P&P 1: The study manual or handbook should include the following:
- Definition of *adverse event*
- Reporting requirements
- Reportable adverse events
- Procedures for review of reported adverse events
- Procedure for reporting adverse events
- Procedure for distribution of reported adverse events to clinics

P&P 2: List events reportable to local or parent IRB, including the following:
- Death
- Life-threatening event
- Event resulting in disability or impairment
- Event requiring treatment
- Event resulting in hospitalization or prolongation of a hospital stay
- Congenital anomaly
- Cancer
- Event considered to decrease the benefit-risk ratio
- Event requiring a change of consent documents
- Breach of enrollment criteria
- Treatment errors or misadventures

- Treatment overdose or underdose
- Unexpected event that is adverse, regardless of severity
- Any event considered to be related to or induced by a study procedure
- Any event reportable to the FDA
- Falsification of data
- Patient complaint regarding adequacy of consent
- Patient complaint regarding adequacy of care

P&P 3: Specify background adverse events considered to be part of the natural course of disease and unrelated to study procedures.

P&P 4: Determine expectation of IRBs for reporting background adverse events; comply with reporting procedures.

Comment

IRBs may not require reports of adverse events considered to be due to the natural course of disease.

P&P 5: In regard to P&Ps 3 and 4, establish procedure to require reports if in doubt as to cause.

P&P 6: Review required reporting procedures with study investigators and monitor for compliance.

P&P 7: In multicenter trials, clinics should forward reports of adverse events to the CC as they are filed with local IRBs; have clinics provide the CC with copies of correspondence to and from local IRBs.

P&P 8: In trials involving INDs, set up procedures to:

- Ensure compliance with FDA reporting requirements
- Ensure filing of safety reports within the allotted time
- Ensure filing of safety reports by the holder of the IND (see **investigational new drug safety report**)
- Ensure distribution of safety reports to all participating clinics
- Ensure distribution of safety reports to all IRBs

P&P 9: In multicenter trials, set up procedures in the CC for distribution of serious and unexpected adverse events to all clinics and their respective IRBs.

P&P 10: Make certain there is a documented audit trail for receipt of adverse events at the CC and for transmission of reports of adverse events to clinics and to their respective IRBs.

P&P 11: Provide clinics with written instructions for timely reporting of serious or unexpected adverse events.

P&P 12: Monitor for compliance to reporting of serious and unexpected events within the required time from discovery.

Comment

Many IRBs require reports within 3 working days of discovery or occurrence.

P&P 13: Set up procedures for periodic review of reported adverse events.

P&P 14: Ensure that the review in relation to P&P 13 is by a competent group; requirement of competency to include numerator and denominator data needed to calculate and compare rates, access to results by treatment group, and being unmasked to treatment assignment.

P&P 15: Set up procedures for internal review of all serious and unexpected events.