COLUMBIA UNIVERSITY INSTITUTIONAL REVIEW BOARD POLICY

REPORTING TO THE IRB OF UNANTICIPATED PROBLEMS INVOLVING RISKS

I. SCOPE:

This Policy applies to all human subjects research conducted by Columbia University ("Columbia") faculty, staff and students, including behavioral, biomedical and social sciences research, and sets forth Columbia's requirements for the reporting of unanticipated problems involving risks to subjects or others that arise in the course of conducting such research.

Reporting of Unanticipated Problems (including adverse events) by investigators to sponsors or government agencies is not covered by this Policy.

II. EFFECTIVE DATE: January 24, 2008

This Policy supersedes Columbia's Adverse Events and Unanticipated Risks Reporting Policy, dated April 13, 2004.

The Policy was updated to emphasize the need to report both serious and non-serious unanticipated problems that involve risks to subjects or others and are related to the research. The previous policy focused on the reporting of "risks to subjects from serious and unanticipated adverse events".

III. BACKGROUND:

Federal regulations [45 CFR 46.103(b)(5) and 21 CFR 56.108(b)] require that institutions engaged in human subjects research have written procedures to ensure the prompt reporting to the appropriate IRB of the occurrence in such research of unanticipated problems involving risks to subjects or others. In addition, federal regulations [45 CFR 46.109(e) and 21 CFR 56.109(f)] require the IRB to conduct continuing review of research at intervals appropriate to the degree of risk involved in such research, but not less than once a year. To ensure that the risk/benefit ratio of studies continues to be acceptable, the IRB must take into account the occurrence of unanticipated problems.

The U.S. Department of Health and Human Services ("HHS") issued a "Guidance on Reviewing and Reporting Risks to Subjects or Others and Adverse Events" on January 15, 2007 (the "HHS Guidance"). The HHS Guidance can be found at http://www.hhs.gov/ohrp/policy/AdvEvntGuid.pdf. In addition, the U.S. Food and Drug Administration ("FDA") issued a "Draft Guidance on Adverse Event Reporting" on April

9, 2007 (the "FDA Draft Guidance" and, together with the HHS Guidance, are referred to as the "Guidances"). The FDA Guidance can be found at http://www.fda.gov/cber/gdlns/advreport.pdf. This Policy is based on the federal regulations and these Guidances.

IV. DEFINITIONS:

"Adverse Event": any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, 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.

"Monitoring Entity": the group that is responsible for overseeing the safety of all subjects enrolled in the study in accordance with the protocol (e.g., a Data Safety Monitoring Board (DSMB), a Data Monitoring Committee (DMC), a coordinating or statistical center, or a sponsor).

"Unanticipated Problem": any incident, experience or outcome involving risk to subjects or others in any human subjects research that meets all of the following criteria:

A. unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;

B. related or possibly related to participation in such research (i.e., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and

C. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

V. POLICY:

All Unanticipated Problems should be reported to the designated IRB of record for the protocol to which the Unanticipated Problem relates:

A. promptly, but not later than one week following the occurrence of the Unanticipated Problem or the Principal Investigator's acquiring knowledge of the Unanticipated Problem; and

B. at the time of continuing review,

in each case in accordance with the procedures described in Section VI below.

Only Unanticipated Problems need to be reported. Although the Guidances also refer to Adverse Events, an Unanticipated Problem may or may not be an Adverse Event and an Adverse Event may or may not be an Unanticipated Problem. **Only Adverse Events that meet the criteria of an Unanticipated Problem are reportable to the IRB.**

Examples of Unanticipated Problems include, but are not limited to, in addition to certain Adverse Events, breaches of confidentiality (such as loss of a laptop with private identifiable information about subjects), errors in the dosing of medication (regardless of whether the dosing error was more or less than the prescribed amount), and safety monitoring procedures that were not conducted or their results lost or inadvertently destroyed.

For further guidance in determining whether an event is an Unanticipated Problem, and/or an Adverse Event, see the Appendix: "Understanding the Relationship Between Adverse Events and Unanticipated Problems".

VI. PROCEDURES:

A. At the time of the Occurrence of an Unanticipated Problem:

Each Unanticipated Problem should be reported to the designated IRB, whether or not (a) it is serious or non-serious or (b) it occurs at a site at which a Columbia investigator is conducting the research (an "Internal Site"), or a site at which a non-Columbia investigator is conducting the research (an "External Site").

For research conducted at an Internal Site, the Columbia investigator should make the determination as to whether an incident, experience, or outcome constitutes an Unanticipated Problem.

For research conducted at an External Site, an incident, experience, or outcome generally should be reported to the IRB only if a Monitoring Entity or an External Site investigator has determined that it constitutes an Unanticipated Problem and so notifies the Columbia investigator.

Each Unanticipated Problem should be reported to the IRB using the Unanticipated Problem Report module in RASCAL, whether or not the Unanticipated Problem occurred at an Internal Site or an External Site. If the latter, any report received by the Columbia investigator with respect to the Unanticipated Problem should be attached in RASCAL.

The investigator must conclude in the RASCAL Unanticipated Problem Report whether the protocol and/or consent form(s) should be modified as a result of the Unanticipated Problem. If the protocol and/or consent document(s) requires a revision, a Modification must be submitted in RASCAL.

B. At the Time of Continuing Review of a Protocol

At the time of continuing review of a protocol, a Columbia investigator should submit a summary of all Unanticipated Problems that occurred during the review period and since the beginning of the study. The summary for each Unanticipated Problem should include:

1. the number of subjects who experienced the Unanticipated Problem;
2. the investigator's determination of whether or not the Unanticipated Problem was serious;
3. the investigator's determination of the Unanticipated Problem's relationship to the study procedures (e.g., definitely related, probably related, or possibly related).

If the study is a multi-center study and is subject to oversight by a Monitoring Entity, a current report from the Monitoring Entity may be submitted in lieu of the summary of Unanticipated Problems described above. The current monitoring report must indicate the date of the review and the Monitoring Entity's assessment of the data reviewed. If not described in the data safety monitoring plan submitted to the IRB, the report should also identify what information was reviewed.

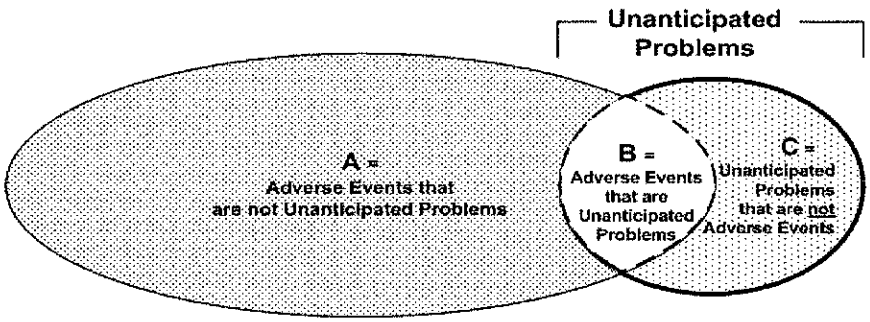
Any Monitoring Entity reports that have not been previously submitted to the IRB should also be included with the continuing review submission. (Note that such reports should be routinely reported promptly to the IRB and submitted in RASCAL as a modification to the protocol if a submission for continuing review will not occur within 30 days of the receipt of a Monitoring Entity report).

The summary or the Monitoring Entity report should be attached as a separate document in RASCAL that is clearly identifiable as a summary relating to Unanticipated Problems or a recent monitoring report

Appendix: Understanding the Relationship Between Adverse Events and Unanticipated Problems

Many sponsors and investigators, particularly in clinical research, have historically focused on the reporting of adverse events rather than Unanticipated Problems. This Appendix provides additional insights into the relationship between Adverse Events and Unanticipated Problems.

The diagram that follows, provided by the Office of Human Research Protection (OHRP), helps conceptualize that relationship.



Under 45 CFR part 46: Do not report A; Report B and C.

The diagram illustrates three key points:

- The vast majority of Adverse Events occurring in human subjects are not Unanticipated Problems (area A).
- A small proportion of Adverse Events are Unanticipated Problems (area B)
- Unanticipated Problems include other incidents, experiences, and outcomes that are not adverse events (area C).

The key question regarding a particular Adverse Event is whether it meets the three criteria described in Section IV.A. and therefore constitutes an Unanticipated Problem.

The flow chart below (from the OHRP Guidance) provides an algorithm for determining whether an adverse event represents an Unanticipated Problem that needs to be reported under HHS regulations at 45 CFR Part 46.