Sheet 18: GUIDELINES FOR NIH INTRAMURAL INVESTIGATORS AND INSTITUTIONAL REVIEW BOARDS ON DATA AND SAFETY MONITORING

Introduction

On June 5, 2000, NIH issued "Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials", which, together with an earlier policy for Phase III and IV trials, issued in June, 1998, requires Principal Investigators to submit a general description of a data and safety monitoring plan as part of their research protocols.

These policies may be found at http://grants.nih.gov/grants/guide/notice-files/not98-084.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html. **They are effective as of October, 2000 and apply to investigators in the intramural research program as well as to extramural investigators**.

The following are basic guidelines on data and safety monitoring requirements for protocols developed by investigators in the NIH Intramural Research Program (IRP), effective immediately and until further notice.

1. General

There are four important elements involved in data and safety monitoring:

(a) The Principal Investigator (PI) must include a data and safety monitoring plan in each new protocol;

(b) The IRB must approve the plan and determine what kind of safety monitoring process (if any) is required: e.g., PI monitoring only; a single independent monitor, or a data and safety monitoring board (DSMB);

(c) The Institute Clinical Director is responsible for appointing an independent monitor or convening a DSMB (if an applicable Institute DSMB does not already exist - see 4, below);

(d) The PI is responsible for providing all required data to the individual monitor or the DSMB and for acting upon any findings made by the DSMB or monitor.

2. Protocol Monitoring Plan

Principal Investigators (PIs) must address data and safety monitoring by providing a data and safety monitoring plan in all protocols submitted to NIH intramural Institutional Review Boards (IRBs). This plan may be

included in the section in the protocol that addresses reporting of adverse events. See Information Sheet #5 "Guidelines for Writing Research Protocols." For many phase I and phase II trials, independent monitors or data and safety monitoring boards (DSMBs) may not be necessary or appropriate, particularly if the protocol involves no more than minimal risk. Continuous, close monitoring by the PI, with prompt reporting of serious adverse events to the IRB (and others, as appropriate) may be adequate. However, **at the time of initial review, the PI and the IRB must agree on the appropriate level of monitoring required for the protocol under consideration. Existing protocols without an adverse event reporting/data and safety monitoring section should be amended no later than at the time of IRB continuing review.**

3. Points to consider in deciding what kind of monitoring is appropriate

The IRB should determine what type of monitoring is appropriate for each protocol based on the level of risk and the number of subjects to be studied. Its determination should be recorded in the IRB meeting minutes.

Protocols that typically require a DSMB include:

- Protocols that generate blinded/randomized data
- Multicenter protocols presenting more than minimal risk to subjects
- Protocols using gene transfer or gene therapy methodology.

Protocols that *may* require a DSMB **or** an individual independent monitor include:

- Protocols that pose more than minimal risk to the subjects
- Protocols that the sponsoring IC believes require special scrutiny because of high public interest or public perception of risk

4. Institutional Responsibility for DSMBs

Institute Scientific Directors are responsible for providing adequate resources and staff support for any DSMB established by the IC.

Institute Clinical Directors are responsible for appointing members of intramural DSMBs. If a trans-NIH DSMB is needed, appointments will be made by the Associate Director for Clinical Research, NIH.

Some NIH intramural programs (e.g., NCI, NEI and NHLBI) already have Institute- or disease-specific DSMBs to review any protocols that their PIs and the IRB decide need this level of monitoring. Other ICs may also elect to form Institute-specific DSMBs to cover all their eligible protocols or may decide to appoint *ad hoc* DSMBs either for single studies or for specific conditions/modalities/treatments (e.g., HIV infection or gene transfer). Once an IRB has decided that a protocol requires an independent monitor or DSMB it is the Clinical Director's responsibility either to refer the protocol to an existing DSMB, or to establish an *ad hoc* DSMB for it.

Intramural protocols may also be subject to monitoring by DSMBs appointed by non-NIH sponsors of multicenter trials. This does not preclude an intramural IC from having the protocol reviewed by an intramural DSMB as well.

5. Membership of Intramural DSMBs

DSMB members are expected to include clinical trial experts, biostatisticians and physicians and others knowledgeable about the disease/treatment under study. Members should not have professional or financial interests dependent on the outcome of the protocol, and should not be employed by the NIH Institute whose studies are under review, unless otherwise justified and approved by the IC Scientific and Clinical Director.

6. Responsibilities and Functions of DSMBs and Independent Monitors

Although the responsibilities and functions of DSMBs and independent monitors are not mandated by regulation, their role in protecting the safety of human subjects is critical, and includes:

- Examining safety and efficacy data and other records from protocols on an explicitly defined schedule

- Making findings and interpreting data including reporting information to the PI, IRB and IC Clinical Director about continuation, modification, suspension or termination of protocols based on observed beneficial or adverse effects of any of the experimental treatments under study

- Reviewing the general progress and conduct of the study.

DSMBs generally meet at regular intervals on a schedule that will be determined by the types of protocols being monitored. Additional meetings may also be scheduled when necessary.

Intramural DSMBs are expected to provide findings resulting from each of their meetings to the PI, the IRB and the IC Clinical Director.

7. Interactions of PIs and NIH IRBs with Intramural DSMBs and Independent Study Monitors

The PI is responsible for providing the DSMB or independent study monitor with any data or other information it requires in order to make its assessments. The PI must report serious, unexpected adverse events and deaths related to the protocol's experimental procedures to the DSMB or independent study monitor at the same time as they are reported to the IRB, the IC Clinical Director and other NIH officials.

IRBs should review DSMB or independent monitor reports as they are received, and not wait to do so until the time of continuing review. They and the PI should act promptly on any findings indicating the need for an amendment to the protocol or affecting the continuation of the protocol. Likewise, PIs and the IRB should notify the DSMB promptly of any protocol amendments they generate.

If PIs or IRBs have any questions about these interim guidelines, please telephone the Office of Human Subjects Research (OHSR), 301-402-3444.