

In March, 1998, a subcommittee of the NIH Human Subjects Research Advisory Committee (HSRAC) was constituted to examine what information is usually disclosed to research subjects enrolled in Clinical Center studies where the research design prevents them knowing at the outset the experimental treatment or drug they will receive. Such studies are normally called randomized, controlled or placebo trials and the subjects, and often the investigators as well, are "blinded" to certain information in order to reduce bias.

The HSRAC subcommittee was given three tasks (see headings below), and after evaluation, provided the following report and offered recommendations which the full HSRAC endorsed in July, 1998. The subcommittee recommendations are provided as guidance for investigators and IRBs.

1. Review Clinical Center consent documents used in randomized, blinded studies to evaluate language generally used about unblinding.

The subcommittee reviewed 41 consent documents from active Clinical Center protocols that included blinded design. Some did not discuss blinding in the consent at all. Some described blinding in language such as "neither you nor your doctor (health care providers) will know which treatment you are on." A few indicated that another person, such as a pharmacist in the NIH pharmacy would have this information. In a few consent documents, a rationale was given for blinding "so that the effectiveness of the drug can be accurately evaluated" or "to maintain an equal expectation of benefit between two groups." In a few cases, it was added that this practice (of blinding) "respects the sacrifices made by all of the patients who participated in early stages of the trial. If the results are compromised by premature disclosure of results, their sacrifice, whether of risk, pain, or difficulty, might have been in vain." Fewer consent documents mentioned when or in what conditions information about treatment assignment would be provided to participants at the completion of the study. In a few documents, statements about the timing of sharing information suggest to subjects that they might receive information at the completion of their involvement (rather than at the completion of the study), e.g. "After you have completed the study, we will share this information with you"; or "This information may be divulged to you after testing is complete." Only a few consent documents made any reference to the possibility of breaking the blind in the event of a medical emergency.

Subcommittee Recommendations

In studies that employ a randomized blinded approach, both randomization and blinding should be explained in simple terms in the consent document. The explanation should include the meaning of randomization, placebo (if used), and blinding; why these methods are being used; who has the ability to identify treatment assignments (who has the code); when and in what conditions the blind may be broken; and when information about treatment assignment will be shared with the subject. It should be made clear whether information is to be shared at the completion of the study rather than when the subject personally completes the study.

2. Determine if it is appropriate ever, and in what circumstances, to permit unblinding before the end of the study.

Random assignment and blinding are methods used in clinical trials to reduce bias and enhance study validity. Both require justification, however, because when randomized and blinded, subjects have no say in their choice of experimental treatment nor do they have information about what experimental treatment they are receiving. In addition, many studies have documented that in blinded trials, subjects and investigators often can guess (more frequently than by chance) whether they are on active drug or placebo. In the scientific design and review of a given protocol, the necessity and adequacy of blinding and randomization

should always be assessed.

Once blinding is chosen as an appropriate method for a particular protocol, there are two main ethical concerns: 1) information about which intervention the subject is receiving may be relevant to his/her autonomous decisions; and 2) information about which intervention the subject is receiving may be important in managing an adverse event or a medical emergency.

With respect to the first concern, if subjects consent to the study and its purpose, they may also consent to suspend knowledge about which intervention they are receiving until study completion or some other predetermined timepoint. To consent, they should understand explicit information provided to them about blinding (as described in #1 above) and agree to the suspension of knowledge. The subject who does not agree to suspend knowledge until study completion should not be included in the study.

With respect to the concern about subject safety, knowledge of which medications the subject is receiving may be relevant to treating adverse events or other medical emergencies. Therefore, investigators should consider these issues in advance and explicitly outline in the protocol the conditions in which adverse events would trigger the breaking of the blind. In some cases, for example, knowing the medication would not alter the management of an emergent or adverse event, whereas in other cases, such knowledge would make a difference.

Subcommittee Recommendations

To balance the need for scientific objectivity with respect to a research subject's need for information to make autonomous decisions, investigators should give subjects adequate information about randomization and blinding (as described in recommendation #1) and ask subjects to consent to a suspension of knowledge about their experimental treatment assignment until the completion of the protocol.

To balance the need for scientific objectivity with the concern for subject safety, investigators should consider in advance the conditions in which a blind may be broken to treat an adverse event. Specifically, they should include a description in the protocol of where the code is located, the circumstances (if any) in which the code will be broken, who will break it, how the information will be handled (i.e. will the investigator, the subject, the IRB, and the treating physician be informed?), and how breaking of a blind will influence analysis of the data. The subject should also have information about whom to notify in the event of an emergency. The IRB should be satisfied that the plan provides for adequate protection of subject privacy.

3. Consider in what circumstances it is appropriate for an IRB to receive information about which subjects are on active drug or placebo.

The IRB is responsible for knowing that subject welfare is protected and that "the research plan has adequate provisions for monitoring data collected to ensure the safety of subjects" [45 CFR 46.111(6)]. The IRB also has a responsibility to assure that the proposed research methodology will provide useful and valid information. In this light, all protocols which involve an experimental intervention, including those that involve randomization and blinding, should have a predetermined rating system for evaluating adverse events (this could be a graded toxicity scale such as that used by the NCI or a simple dichotomous definition of serious vs. non-serious adverse events as dictated by the FDA). The IRB should satisfy itself at the initial review of a protocol that procedures for identifying and reporting adverse events are planned and adequate. In some cases, even for single site Clinical Center studies, a Data and Safety Monitoring Board (DSMB) may be an appropriate mechanism for assuring regular review of research data. In trials that do not have a DSMB, the details of what incidence or severity of foreseeable adverse events would trigger modifications in the trial or in the management of an individual subject (including in what circumstances the blind would be broken) should be spelled out, as well as a mechanism for dealing with unpredictable events. These issues are important to the IRB both for the safety of the individual subject as well as to allow evaluation of risks and informed consent for all other (and future) subjects of the study. After the

occurrence of an adverse event, while considering appropriate management of the subject, as well as the risk-benefit analysis and informed consent of other subjects, the IRB may determine in some cases that breaking the blind is unnecessary. In other cases, the IRB may decide that the information about experimental assignment is vital to their deliberations.

Subcommittee Recommendation

For protocols that involve an experimental intervention, including but not limited to those which employ randomization and blinding, the IRB should be satisfied that the plan for monitoring subjects and identification and reporting adverse events is appropriate and adequate. The IRB should be informed of the method that will be used to rate adverse events, the plan for managing adverse events, and how the protocol might be modified for predictable or unpredictable adverse events. When an adverse event is reported to it, the IRB should decide whether or not maintaining the blind jeopardizes the welfare of the individual subject and/or other subjects on the same study.