trials. Trials that must be registered include any project in which an intervention and a comparison group are studied to determine the effect of the intervention on a health outcome (9). Phase I trials have generally been excluded from the registry (10). It is the responsibility of lead sponsors, working together with investigators, to register clinical trials (11).

Obligations of Monitors

The monitor of a clinical investigation confirms that the study is conducted according to the protocol developed by the investigator and sponsor, and according to FDA regulations. This is accomplished by meeting with the investigator and the research staff before a study begins and confirming the adequacy of the investigator's facilities. The monitor makes periodic reviews of the investigator's source documents, case report forms, and required reports. Problems with the study must be documented, and corrective actions taken.

Obligations of Investigators

Similarly, an investigator's responsibilities are contained in the FDA regulations. His/her agreement to conduct an investigation in accordance with regulations and the clinical protocol is documented when the investigator signs form FDA 1572, which is filed with the IND application. In 2000, the U.S. NIH issued a directive requiring that federally funded clinical researchers provide evidence of training on the protection of human research participants and on GCP. Briefly, the investigator must obtain IRB approval for the protocol, the consent document, and recruiting materials used to identify volunteers. He/she must obtain approval for study amendments and file regular reports with the IRB. The investigator must keep immaculate records and must report serious and unexpected adverse events to the sponsor and the IRB. The investigator must administer the vaccine and maintain records accounting for the product disposition. He/she is responsible for educating volunteers and obtaining written informed consent before volunteers become involved in the study. The investigator is obligated to store records, and allow FDA representatives to inspect the study records.

Institutional Review Boards

An IRB is a group designated by an institution to review and approve biomedical research involving humans. IRBs are responsible for the well being of subjects involved in clinical trials. The board includes at least five members, at least one who is not a scientist, and one who is not affiliated with the institution. The IRB reviews protocols, investigator's brochures, consent forms, recruiting materials, and additional safety information. The membership of an IRB, standard operating procedures, review of research, voting and quorums are defined in part 56 of 21 CFR.

Record Keeping and Product Accountability for Clinical Trials

Compulsive record keeping is an important component of GCP. The need for privacy and protection of medical records has led to regulations under the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Restraints on the use of medical information for research were imposed in 2003. The new privacy rules are under debate as regulators attempt to balance the public interest in research with the public interest in privacy (12,13).

Both investigators and sponsors should retain the same records. Case report forms are uniform at all the sites conducting the study, and allow the sponsor to look at the same information in the same format from different sites. The case report forms may be used for data entry and analysis and should be designed to efficiently capture the data points that precisely correspond to the aims and endpoints of the protocol. ''Source documents,'' those records on which the information about a participant is first recorded, may be used for some studies. The type of information to be collected may vary with the protocol, but in general it would include subject identification, protocol name and number, sponsor's name, date of participant's visit, procedures and tests completed, concomitant medications, occurrence of adverse experiences, and the name of the person entering the information and the date. Corrections to the study records must be initialed and dated.

In 1997, the U.S. FDA established regulations about the use of electronic records in clinical trials (21 CFR part 11). The regulations permit use of electronic signatures. Investigators have the option of maintaining records as paper files or electronic files. The electronic record must provide an audit trail, that is, a record of who enters or changes data and when (14). Teleforms for electronic database entry and on-line case report forms have replaced paper forms for most studies.

Investigators usually develop a protocol-specific quality management plan to ensure the correctness of the data collected. A sponsor should have a policy about monitoring case report forms that indicates how frequently forms are to be monitored and how intensively. Monitors compare source documents with case report forms, looking for inconsistencies, errors, and appropriate signatures.

In addition to maintaining clinical records, investigators are required to maintain records for the receipt and disposition of the experimental product. The records should include the name of the material, its IND number, its condition, the lot number, date, and source. Records should show the name of persons who received the study vaccine and what was done with extra doses. Each dose must be accounted for. To assure that the experimental product is not tampered with, vaccine materials should be stored in a secure refrigerator, freezer, or cabinet.

Reporting Adverse Experiences

The NIH has developed policies for safety monitoring of all studies that evaluate investigational drugs and biologics. These policies require that there is a system for oversight and monitoring of clinical trials. The mechanism of oversight depends on the risk and complexity of the trial and may be a full data and safety monitoring board, a safety committee, or an individual independent safety monitor.

FDA regulations require investigators to report all adverse experiences to the sponsor of a study. If the experience is serious or unexpected, the event must be reported promptly to both the sponsor and the responsible IRB. A serious adverse experience is ''any experience that is fatal or life-threatening, is permanently disabling, requires or extends inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.'' An unexpected adverse experience is ''any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure; or, if an investigator brochure is