NIH Phase III Clinical Trials Monitoring: A Survey Report

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Executive Summary

In 1994, the NIH Office of Extramural Research established a Committee to review the oversight and management practices of Phase III clinical trials by NIH Institutes and Centers (ICs). The Committee identified eight key issues, developed a questionnaire, and surveyed NIH staff responsible for a representative sample of the 470 clinical trials then in progress. A total of 130 trials--large and small, single center and multicenter, funded through grants, cooperative agreements, and contracts were surveyed.

The survey showed that funding mechanisms influence the way clinical trials are managed. For the most part, large multicenter trials supported by either cooperative agreements or contracts had effective staff oversight. Grant-supported trials, on the other hand, presented an uneven picture. This probably reflects a different degree of direct involvement by NIH staff with investigator-initiated studies.

Treatment Allocation. The great majority of the trials--including virtually all large multicenter studies funded by cooperative agreements and contracts--used masked (blinded) random allocation, and this randomization was almost always totally unpredictable. Furthermore, most trials analyzed data using the "intention to treat" criterion. Finally, the individual or group performing the major outcome assessment was blinded to treatment allocation in two thirds of the surveyed trials.

Data and Safety Monitoring Board (DSMB). Most multicenter studies and a third of single-center trials had these external oversight bodies. Among those that did not, the majority were behavioral or lifestyle studies.

Quality Assurance. Almost all multicenter trials had some form of quality assurance program. However, both trial type-single center or multicenter--and funding mechanism greatly influenced the depth of the program.

Community Trials. Forty trials had satellite sites in addition to primary trial sites. Overall, these trials involved large study populations, and most were funded through cooperative agreements and/or contracts. Criteria for monitoring and review were generally the same for satellites as for primary sites.

NIH Staff Involvement. NIH staff were much more likely to be actively involved in trials supported by cooperative agreements and R&D contracts than for clinical trials supported by grants, as well as for clinical trials conducted at multiple centers than at a single center.

Informed Consent. Most clinical trials had developed standard consent materials for use across participating sites, and most multicenter trials had developed centralized procedures to teach sites how to use these materials. Emerging trial information was usually presented to subjects informally, through the physician or other study care provider, although some studies had developed formal channels for keeping participants informed of new developments.

Data Access. While an IC's rights to access trial data are assured by Federal regulations, data in the possession and control of NIH constitute Government records that are subject to the Freedom of Information Act (FOIA) -- with the proviso that, in accord with the Privacy Act, patient identifiers as well as proprietary data are first removed before the data are released.

Approximately 45 percent of ICs did not routinely access trial data while the trial is ongoing. Almost one third of the trials reported that the IC would obtain data in cases of overriding public health concerns. Some 60 percent accessed raw data at the end of the trial. About 40 percent of the ICs actually took possession of data tapes at the end of the trial.

Computer-assisted Information Transfer. Computers were most commonly used for automated participant registration and data analysis. Data security was assured by authorized access, log-in security, or encryption. Almost all trials used periodic data back-up to ensure data integrity, and most reported taking measures, such as double data entry, to validate data entry. However, fewer than 60 percent employed an audit trail to document modifications in data entries.

RECOMMENDATIONS

- ICs should consider using a centralized system such as a data service center to monitor entry criteria and randomize treatment participants.

- All trials, even those that pose little likelihood of harm, should consider an external monitoring body.

- ICs should review their clinical trial quality assurance programs and monitoring procedures to determine whether current practice(s) include, at the very least, on-site monitoring of all centers on some regular basis, central monitoring of key outcome data, and a data quality program to identify the type and quantity of data checking conducted during on-site visits. Every data coordinating center should be subject to regular site visits.

- In view of the numerous advantages offered by community trials, NIH staff should examine ways to maximize their

impact. Possible areas for reevaluation include the flexibility of trial requirements, the funding of satellites, transportation problems, and the identification of components that do not require on-site monitoring.

- Because of the distinct differences in the oversight of grant-supported versus cooperative agreement or contract-supported clinical trials, ICs should review their policies concerning award mechanisms for Phase III clinical trials.

- Multicenter trials that are likely to recruit from diverse populations should develop strategies that ensure appropriate informed consent across sites. Consent forms need to pay close attention to issues of language, cultural factors, and level of difficulty.

- NIH staff and trial investigators should identify strategies that simultaneously protect patient confidentiality and make it possible to track patients, especially for long-term trials.

- Each IC should review its policy and practices regarding IC access to trial data, to determine whether current practice(s) provide sufficient opportunity to monitor data while at the same time appropriately protecting the awardees' data from premature public disclosure.

- ICs should identify issues of data security, and validation germane to each individual trial at the time the study protocol is developed. NIH should also provide study sponsors with technical assistance in the form of workshops, including cost-benefit studies of trial automation.

BACKGROUND

As FY 1994 ended, the NIH was supporting 470 Phase III clinical trials.[1],[2] These trials--almost all in the extramural program--varied enormously in size, complexity, and subject matter. They included a cancer screening trial in 148,000 subjects at 10 research sites, a trial of nutritional therapy for rare enzyme disorders in 142 patients recruited from 61 sites, and a trial of cochlear implants in 110 children conducted at a single site. The Mycoses Study Group, with nearly 4,000 subjects, had 32 main sites and 23 community affiliates; chemoprophylaxis for Lyme disease was being tested at two centers in New England. The median number of subjects in these clinical trials was 365, the median number of sites, 25.

How does NIH oversee and manage this challenging research portfolio? In 1994, the NIH Office of Extramural Research (OER) undertook a review to answer this question. The review, which focused on the extramural program, was conducted in stages. It began with a snapshot view of 10 selected trials, followed by an inventory of all Phase III clinical trials.[3]

In June, 1994, OER convened the NIH Working Committee on Clinical Trial Monitoring. The 24-member Committee is made up of representatives from the Institutes and Centers (ICs), chosen for their expertise in various aspects of clinical trials, including study design, biostatistics, ethics, and computer transfer of trial information. (Committee members are listed in Appendix I.)

The Committee was charged with identifying significant areas to be addressed in the review. In a series of biweekly meetings, the Committee decided on eight such areas:

- Treatment allocation
- Data and safety monitoring boards
- Quality assurance
- Community trials
- NIH staff involvement
- Informing patients
- Publications and data access

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[1]A Phase III clinical trial, as defined in the Guidelines for the Inclusion of Women and Minorities as Subjects in Clinical Research, is any broadly based prospective study evaluating an experimental intervention with a control or standard, or comparing two or more existing treatments or interventions where the outcome of the study is likely to contribute to change in either standard of care or public health policy.

[2]The figure 470 came from information supplied to the Office of Extramural Research by Institutes and Centers.

[3]An NIH Clinical Trial Registry is being developed under the leadership of the National Library of Medicine and the Office of Research on Women's Health.

- Publications and data access
- Computer-assisted information transfer

The Committee elected to explore these issues by conducting a survey of NIH staff responsible for specific clinical trials. To develop a questionnaire for the survey, the Committee split into eight working groups--one for each area of focus--and recruited additional members from throughout NIH.

Questions were developed by each working group and approved by the full Committee. The survey instrument, which defined terms and provided sample answers, was tested in a pilot study, and the responses were analyzed by an independent survey researcher. Although the NIH staff responding to the questionnaire were encouraged to contact study leaders for additional information, it is always possible that study results reflect misinterpretation of some questions or unfamiliarity with certain aspects of funded trials, especially those conducted through mechanisms that limit NIH program staff involvement.

To obtain a representative sample of clinical trials, the Committee developed a stratified sampling plan. This plan took into account the size of each IC's clinical trial portfolio, the various types of funding mechanisms as well as the differential use of funding mechanisms by the ICs.

A total of 130 extramural trials were surveyed. However, the survey results were calculated on the basis of 114 trials, partly because several of the surveyed trials were later determined not to be Phase III trials. Although the percents quoted in the survey results were not adjusted to account for the stratified sampling scheme, the sampling plan allowed the Committee to make an assessment of the selected clinical trials and draw inferences about overall management and oversight.

Funding Mechanisms

NIH uses two major categories of awards, assistance and procurement. In assistance awards, NIH acts as patron or partner; in procurement awards, NIH acts as purchaser.

The goal of assistance awards, which include both grants and cooperative agreements, is to accomplish a public purpose authorized by Federal statute 31 U.S.C. Section 6303-05. With a cooperative agreement, NIH program staff is expected to make substantial contributions to the trial--providing technical assistance and guidance to, or coordinating or participating in, programmatic activities. With a grant, the role of NIH staff is limited to basic stewardship responsibilities. The grants category includes the traditional, individual-investigator-initiated research project grant (R01) as well as the program project grant (P01), which often marries clinical and basic research components. Other types of grants fund specific types of Centers (for example, P50 for specialized centers, P60 for comprehensive centers).

Procurement awards--research and development (R&D) contracts--are used when the principal purpose of the transaction is to acquire property or services for the direct benefit or use of the Federal government. Clinical trials supported by R&D contracts typically are planned, initiated, and controlled by NIH staff. The NIH project officer specifies protocols, tests, and procedures, and makes the primary study decisions.

The use of grants, cooperative agreements and contracts differs greatly among the various ICs. Some Institutes (e.g., NEI, NHLBI, NIA, NIAAA, and NIAID) use cooperative agreements and contracts almost exclusively. Some Institutes (e.g., NIAMS, NIDCD, and NINDS) support clinical trials mainly through grants. Other Institutes (e.g., NCI, NIDDK, and NICHD) use a mix of award mechanisms.

The 470 Phase III clinical trials were funded as follows:

Cooperative agreements	180
Research grants	170
Contracts	85
Intramural and Interagency	35

The 114 sampled trials were distributed as follows:

SURVEYED CLINICAL TRIALS
TRIAL TYPE AND MECHANISM OF SUPPORT

	Funding Mechanism				
	Individual Grant	**Program Project Grant**	**Cooperative Agreement**	**Contract**	**Cooperative Agreement & Contract**
	N=(51)	(10)	(37)	(9)	(7)
Single Center (42)	29	9	3	1	0
Multi-center (72)	22	1	34	8	7

SURVEY FINDINGS

1. Treatment Allocation

The questionnaire addressed three aspects of treatment allocation critical to a clinical trial's validity. These are randomization, complete and unbiased outcome ascertainment, and an objective analysis of results.

Randomization

Masked (blinded) random assignment of trial subjects to various treatment groups tends to distribute measured and unmeasured covariables, so that any measured differences are attributable to the treatment. (Special circumstances may, infrequently, justify other, less optimal allocation plans.)

While allocation schemes generally involve individuals, random allocation can also be done for paired organs (e.g., eyes) in an individual when the pairs are equally eligible for treatment. Equally well accepted is random allocation of groups or communities as was done in the NCI-sponsored Community Intervention Trial (COMMIT) for Smoking Cessation.

Occasionally, allocation, though random, can be predicted by investigators, introducing possible biases in either allocation or analysis. For example, an investigator may be aware that certain treatments are limited to sites with special expertise or equipment, or an investigator might even gain access to the randomization list.[4]

The survey revealed that the great majority of the trials (98 of 114) used random allocation.

RANDOMIZATION

Mechanism (n)	Random allocation
Individual grant (51)	75%
Program project grant (10)	80%
Cooperative agreement (37)	97%
Contract (9)	100%
Cooperative agreement & contract (7)	86%
Total (114)	86%

Furthermore, in 86 of these 98 trials, this randomization was entirely unpredictable. This was true for 82 percent of the

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[4]Certain approaches assure balanced numbers and characteristics across multiple clinics yet preserve unpredictable assignment. However, because this aspect is less central to internal validity, it was not assessed in this survey.

randomized trials supported by individual grants, 75 percent of the program project grants, 89 percent of the cooperative agreements, 100 percent of the contracts, and 100 percent of the cooperative agreements plus contracts.

Large multicenter studies funded by cooperative agreements and contracts almost always had randomization that was entirely unpredictable. Grant-supported trials, either individual or program project, were more likely to include nonrandomized allocations. Nonrandomized allocation also occurred in studies involving groups (communities, schools, hospitals), but this was not surprising since group studies often experience problems with limited sample size and agreement to be randomized to control or standard treatment.

In the 16 studies that were not randomized, treatment assignment was controlled by the following:

Investigator preference	7
Participant preference	2
Treatment availability	3
Other	4

Analytical Strategy

A second prerequisite for internal validity is an analysis that is objective. So-called "intention to treat" analysis reports outcomes, both good and bad, that accrue as the result of embarking on the treatment originally assigned--whether or not participants subsequently drop out or "cross over" to another treatment. Analysis by intention to treat is especially important in long-term trials where participants may find it difficult to remain on the study. Intention to treat analysis also provides a better barometer for conditions likely to occur in the practice setting.[5]

Of the 107 responses to this particular survey question, 91 (85 percent) indicated that "intention to treat" was the planned analytical strategy. These included all trials supported by contracts or cooperative agreements, more than three quarters of trials supported by individual grants, and nearly two thirds of the program project trials.

Unbiased Assessment of Endpoints

In assessing the validity of a clinical trial, it is

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[5]"On-treatment" analysis (i.e., according to the treatment actually administered) may be done as to supplement intention to treat analysis, or it may be done as the only analysis. However, on-treatment analysis can give a distorted, and often inflated, estimate of treatment effect. For instance, it would miss participants being switched to the other treatment arm because of side effects. The results of such analysis are not likely to be confirmed either in practice or in other long-term studies.

important to know whether the report includes the outcomes of all participants and whether these outcomes were assessed in an unbiased manner. To be fully objective, outcomes should be gauged with a standard set of criteria, preferably by an individual or group blinded to treatment assignment.

The survey found that the individual or group performing the major outcome assessment was unaware of treatment allocation in 71 of 108 surveyed trials (66 percent). The figures were 89 percent for contracts, 60 percent for cooperative agreements, 59 percent for individual grants, and 40 percent for program projects.

Although 66 percent is a lower proportion than would be expected in large randomized clinical trials, it may be accounted for by the inclusion of small clinical trials in this survey.

2. Data and Safety Monitoring Boards (DSMB)

Data and Safety Monitoring Boards are external oversight bodies, typically appointed by the Director of the funding IC. Members include experts in the specific discipline of the trial and the general area of science, as well as biostatisticians, ethicists, and patient advocates. DSMBs are appropriate for all trials involving potentially harmful interventions and most others as well.[6] Their primary function is to assure, to the extent possible, the safety of study participants and the integrity of the study. They accomplish the former by being familiar with the protocol and accepting the study concept, by proposing appropriate analyses, and by periodically reviewing the developing data on safety and endpoints. They accomplish the latter by reviewing data on such aspects as participant enrollment, protocol-specified patient visits, trial procedures, forms completion, data quality, losses to follow-up, and other measures of adherence to protocol.

DSMBs generally meet first in open session, attended by selected trial investigators as well as NIH program staff/project officers and perhaps industry representatives, and then in closed session where they review emerging outcome data. Should the Board detect evidence of harm or benefit sooner than anticipated, it can recommend that the trial be modified or stopped altogether.

The questionnaire addressed the organization, responsibilities, and operating procedures of DSMBs. Survey findings revealed that 59 of the 72 (82 percent) multicenter trials had DSMBs. Of those without DSMBs, all but five were behavioral or lifestyle studies.

In contrast to multicenter trials, approximately a third of the 42 single-center trials (funded primarily as R01s or P01s) had a DSMB. Among the 27 that did not, 21 were behavioral or

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[6] NIH Guide for Grants and Contracts, June 1979.

lifestyle studies. Some of the remaining six trials are in the process of establishing DSMBs.

In three quarters of the trials--including all contract and some program projects--DSMB members were appointed by the Director of the funding IC; in the rest, they were appointed by the leadership of the trial or of the cooperative group. It is important to note that industry or Food and Drug Administration (FDA) officials were not involved in appointing members. In a few trials (9 percent), the NIH program staff representative was a voting member.

Ideally, DSMB members are in no way associated with the trial. Conflict of interest statements, written or oral, were obtained in over 90 percent of the DSMBs. When conflict of interest was found, the member was either asked to leave the Board or excluded from a particular discussion.[7]

Maintaining confidentiality of interim trial results is a crucial responsibility of the DSMB. In more than 85 percent of trials, trial leaders attended portions of DSMB meetings; however, they were usually not present when outcome data were being discussed. Interim data were never provided to industry representatives and only rarely to FDA officials. Key NIH program staff, however--who were present during closed sessions in about three quarters of the trials--were always aware of the accumulating outcome data.

The DSMB transmits its recommendations and a summary of its deliberations to the funding IC. In nearly half of the trials, the IC was responsible for implementing the recommendations. For the remaining trials, especially those supported by grants, this task belonged to the trial leadership.

Like the clinical trials they serve, DSMBs are very diverse. Most oversee a single trial. We provide two examples of DSMBs that oversee multiple studies.

> Division of AIDS (DAIDS), NIAID: DAIDS has two DSMBs, one for therapeutic trials and the other for prevention trials. Each of them examines the efficacy and safety data accumulating from the trials from several cooperative groups.
>
> Each DSMB reviews four to six trials at every quarterly two-day meeting, scheduling additional meetings or conference calls as necessary. Interim reports on each trial to be reviewed are sent to Board members a few days prior to the DSMB meeting. Questions, issues and clarifications are put to the Study Chair (trial leader) in open session. Then, in closed session, the Board reviews treatment-specific efficacy and safety data and formulates its recommendations

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[7]It is usually up to the funding IC to determine if conflict of interest exists.

to DAIDS, NIAID.

The DSMB Chair informs each trial leader of the Board's recommendations. A summary report (containing no confidential data) is prepared by the DSMB Chair and distributed to DSMB members, the governing committee of the cooperative clinical trials program, and the NIAID.

Cooperative Group Program, NCI: The Cancer Therapy Evaluation Program (CTEP) coordinates 176 Phase III randomized treatment trials in 11 cooperative groups. These trials involve 5,000 investigators at 1,300 institutions.

Typically, one data monitoring committee (DMC) oversees all the randomized trials of each of the 11 cooperative groups. Members are appointed by the Group Chair, and at least one third of the voting members are not affiliated with the cooperative group. Neither the Group Chair nor the group statistician is a voting member. DMC members involved in the leadership of a study are excluded from discussions of outcome data. However, such exclusion does not always apply to physicians who are enrolling patients in a study, since this could eliminate most of the DMC. Interim outcomes are discussed in executive session, which is limited to voting members and NCI program staff.

The DMC provides recommendations to the Group Chair. If the recommendations entail protocol changes, the Group Chair is responsible for preparing and submitting an amendment to CTEP. CTEP must approve the amendment before any change can be implemented.

3. Quality Assurance

A Quality Assurance Program--defined as the philosophy, procedures, and methods for generating, collecting, processing, and analyzing data aimed at ensuring their reliability and validity--should be in place throughout a clinical trial. During the planning phase, quality assurance procedures include review of the research protocol and informed consent documents. During the implementation phase, quality assurance practices will be influenced by the trial structure (single center or multicenter), the scope of the study, and the nature of the intervention being tested. In all cases, however, the essentials include clear definitions of response variables, standardized procedures, and training of clinical trial staff.

The Committee identified numerous elements of quality assurance. The questionnaire addressed: who is responsible for these various elements; whether or not the trial has on-site monitoring; what items in the patient/study record are reviewed during monitoring visits; and, who is responsible for responding to recommendations in the site visit monitoring report.

PERCENT OF TRIALS DISPLAYING SELECTED QUALITY ASSURANCE ELEMENTS (N=114)

Element	Percent Responding "Yes"
Protocol Review	84%
Informed Consent Review	81%
Centralized Review of Endpoints	89%
Centralized Monitoring by Data Center/ Coordinating Center	62%
•Performance Evaluation of Clinical Sites*	86%
•Data Quality Checks of Clinical Sites*	92%
Elements reviewed in patient records**	
•Eligibility	93%
•Endpoints	76%
•Adverse events	79%
•Informed consent	85%
•Treatment compliance	81%
•Randomization	76%
•Transcription errors	73%

*Percentages for these elements are based on the 78 trials for which responses were given.
**Percentages for this section are based on 85 trials.

As this table shows, most of the clinical trials in the survey had some form of a quality assurance program. However, the depth of the program varied, depending in large part on the type of clinical trial and the funding mechanism.

- Protocol reviews were conducted by the funding IC in 73 percent of the trials, by an external group such as the coordinating center in 67 percent, and by the DSMB in 46 percent.

- Informed consent documents were reviewed as a quality assurance measure in 81 percent of the trials. This was in addition to their requisite review by an Institutional Review Board (IRB).[8]

- Ongoing centralized monitoring was carried out by a data center or coordinating center in 62 percent of the trials, and in an additional 10 percent by the funding IC or some external group. However, 28 percent did not have

[8]The NIH does not fund projects without documentation of institutional human subjects review board approval, as required by Federal regulation 45 CFR Part 46.

ongoing centralized monitoring, and these are predominantly single center trials.

- Clinical site performance was evaluated in 67 trials (86 percent) and not evaluated in 11 others; the remainder--primarily single-center sites--responded "not applicable."

- Data quality checks by data center were reported by 92 percent of the clinical sites; 5 percent reported none. (Thirty-three single center trials responded "not applicable" because there are no data centers involved.)

- Ninety-seven trials had on-site monitoring procedures in place. These were usually developed jointly by several parties, including the Principal Investigator (PI), the funding IC, and the coordinating center or the cooperative group.

- In a majority of trials, the coordinating center performed the on-site monitoring. Approximately two thirds of the centers had on-site visits at least annually.

Quality Assurance: Funding Mechanism and Trial Type

The survey data make clear that both trial type--single center or multicenter--and funding mechanism greatly influenced the implementation of quality assurance programs, as well as the funding Institute's role in developing and monitoring these programs. Multicenter trials and trials supported by cooperative agreements and contracts were much more likely than individual grant/single center trials to include some form of quality assurance and site monitoring.

SELECTED QUALITY ASSURANCE ELEMENTS BY FUNDING MECHANISMS AND TRIAL TYPE

	Individual Grant/Program Project		Cooperative Agreements, Contract (N=53)
	Single Center (N=38)	Multicenter (N=23)	
Protocol Review	59%	95%	100%
Informed Consent Review	59%	95%	98%
Centralized Review of Endpoints	72%	91%	100%
Centralized Monitoring by Data/Coordinating Center	14%	73%	89%
Performance Evaluation of Clinical Sites	7%	64%	94%
Data Quality Checks of Clinical Sites	17%	64%	94%
Elements reviewed in patient records			
•Eligibility	31%	77%	92%
•Endpoints	31%	45%	79%
•Adverse events	28%	41%	87%
•Informed consent	24%	63%	91%
•Treatment compliance	31%	59%	83%
•Randomization	31%	50%	77%
•Transcription errors	28%	41%	79%

•For those single center trials with protocol review, the responsibility for conducting the review was shared equally by the funding Institute, the DSMB, and the institution. In multicenter trials, it was the job of the funding Institute and/or an external group such as the cooperative group or the coordinating center.

•In addition, in 30 percent of the trials the funding Institute provided monitoring guidelines. This was more common for multicenter trials (40 percent) than for single center trials (12 percent). In single center trials, it was usually the Principal Investigator who was responsible for developing such guidelines, whereas at the multicenter trials, it was the IC staff.

•In multicenter trials, on-site monitoring was usually the task of the coordinating center, the Institute staff, or their

contractor. In the single center/individual grant trials, it was usually done by the Principal Investigator.

Quality assurance practices were most prevalent in trials funded by cooperative agreements or contracts. Fifty-six percent of those trials had guidelines for on-site monitoring provided by the funding Institute, typically developed by Institute staff and the cooperative group/coordinating center. In 70 percent of them, on-site monitoring visits were conducted by a monitoring center; the visits occurred at least annually in 60 percent of the trials, and were announced less than 8 weeks in advance. In 51 percent of the trials, additional records were selected on-site for review. In 83 percent of the trials, a report of the monitoring visit was sent to the funding Institute; program staff were responsible for reviewing and following up on recommendations in the report.

4. Community Trials

Community-based clinical trials--defined as trials where satellite or affiliate sites contribute data, receive data queries, and are usually site-monitored through a primary site--differ in a number of ways from trials conducted in the more traditional context of a tertiary care center or an academic medical center. Community hospitals or clinics, health centers, private practices, schools, emergency rooms, public or private community clinics, migrant health centers, STD clinics, HIV testing and counseling centers, pharmacies, mobile units, and correctional institutions all qualify as satellites.[9]

Community trials vary considerably in both context and conduct. Some involve screening or baseline visits at tertiary care medical centers, with the actual intervention administered at a community hospital or private practice. In others, all visits take place in a primary care setting.

Forty trials (35 percent of the 114 in the survey) indicated that they had satellite sites in addition to primary trial sites. Overall, these trials involved large study populations. Their median size was 651 subjects and the median number of sites was 20, compared to 245 subjects and one site for trials without satellites. Most were funded through cooperative agreements and/or contracts, with most satellite sites funded through the same source and mechanism as the primary site. A few trials with satellite sites were funded through individual grants; one was funded through a program project grant.

How, the questionnaire asked, do on-site monitoring practices at the primary site differ from those at satellite

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[9]This discussion excludes studies involving randomization of communities and delivery of interventions to communities, villages, tribes, factories, or schools rather than to individuals, e.g., the NCI COMMIT study or the NIDDK Community-based NIDDM Prevention Zuni Youth Trial.

sites? The majority indicated that primary sites and satellites were identical with respect to the responsibility for monitoring, the individuals performing site monitoring, frequency of on-site monitoring, percent of records reviewed, elements of patient records reviewed, written monitoring reports, performance criteria, and the utility of the monitoring report for improving performance.

The following three examples illustrate the range of monitoring practices:

The NCI's Community Clinical Oncology Program (CCOP) is a network of 50 community programs in 29 states, with over 315 hospitals and 2,900 physicians. The Program also funds eight Clinical Cooperative Groups as well as three Cancer Centers which serve as research bases that develop and manage the clinical trials in which the CCOPs participate. In addition to entering approximately 4,000 patients a year into treatment trials, CCOPs enlist some 4,400 subjects each year in high-priority NCI prevention and control trials such as the Breast Cancer Prevention Trial and the Prostate Cancer Prevention Trial. The CCOPs provide access to geographic areas that provide mixes of patients or subjects not always available in university or urban settings.

At least once every three years, each CCOP is audited by representatives of its research base(s), and in addition may be visited by NCI, or an NCI contractor. Such on-site audits include a review of: the use of investigational drugs; compliance with regulations for IRB approval and informed consent; compliance with protocol specifications; quality control and accuracy of data recording; and completeness of reporting of adverse drug reactions. Reports of on-site audits are reviewed by the Clinical Trials Monitoring Branch, NCI.

The NHLBI Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a practice-based, randomized clinical trial of antihypertensive pharmacologic treatments in 40,000 high-risk hypertensive patients, of whom at least 55 percent are African Americans. This trial is intended to compare the effect of diuretic-based treatment and three alternative antihypertensive pharmacologic treatments on the combined incidence of nonfatal myocardial infarction and coronary heart disease death.

The ALLHAT trial is just getting under way. At full scale it will comprise approximately 400 clinical trial sites, including Veterans' Administration (VA) hospitals, university centers, health maintenance organizations (HMOs), and, mostly, community primary care clinics and physicians' offices. Approximately 63 of the sites are VA hospitals across the U.S., organized as a single region under a VA Coordinator. The remaining sites (including 67 university centers) are assigned, primarily by geographical location,

to one of the seven additional regions, each of which is under a Regional Physician Coordinator located at a university center. The recruitment of a clinical site and its assignment to a region is the task of the ALLHAT coordinating center, the Clinical Trial Center (CTC).

The ALLHAT site visit strategy has three components:

(1) Clinical site visits conducted by Regional Coordinators (and ALLHAT staff). The Regional Study Coordinator visits each clinic within the region twice during the first year and at least every other year thereafter. At every visit the Regional Coordinator, using a standard site visit checklist developed by the CTC, reviews regulatory and administrative documents, drug accountability and storage documents, patient recruitment and retention documents, and patient charts (source documents). The review includes patient eligibility and verification of critical study variables. Additionally, the CTC preselects a number of patient records to be reviewed.

(2) Site visits to Regional Coordinators. The CTC, the NIH ALLHAT program staff, and one other Regional Coordinator visit each Regional Coordinator. The focus of the visit, which aims to assess the Regional Coordinator's oversight of the clinical sites within her or his region, is mainly to discuss administrative issues. At times this assessment is conducted by telephone.

(3) Site visits by ALLHAT Program staff. The ALLHAT program staff plan to visit clinical sites or accompany Regional Coordinators on site visits in each region each year. It is important to stress that the strategy for ALLHAT monitoring/audit site visits is still evolving. The philosophy is to remain flexible so as to adapt to the unique features of the study and yet assure the reliability of the outcome data.

The NIAID Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) is a large, community-based clinical research consortium. Its mission is to test interventions that are in wide use or of potential use in primary care settings with underserved populations. It emphasizes studies that assess clinical hypotheses with easily measured clinical endpoints (i.e., progression to AIDS, death).

CPCRA sites include individual medical care organizations, consortia of private physicians, HMOs, community hospitals, community health clinics, and other organizations providing primary care to HIV-infected populations. Though diverse, the community-based organizations supported by CPCRA share the following characteristics: a group of licensed physicians and nurses who provide primary health care to HIV-infected persons; access to a large number of persons infected with HIV, particularly minorities and persons who

use injectable drugs; evidence of substantial experience and expertise in the care and treatment of persons with HIV infection; demonstrable support from the community; and evidence of established relationships with community health care facilities.

CPCRA quality assurance components include 1) internal quality assurance procedures at each clinical site, 2) an external monitoring program, with the CPCRA statistical center conducting data edits to check for incomplete or incorrect data entries, and 3) the on-site external monitoring of clinical data via site visits by the Clinical Site Monitoring Group (CSMG).

Site monitoring visits take place every quarter and last for 5 to 10 days, including side visits to the satellite sites. (Satellite sites are visited at least annually.) This schedule makes it possible to detect problems and correct them while trials are still underway.

The CSMG is responsible for making sure that the investigator fulfills her or his obligations, as set forth in applicable regulations and NIAID policies, and that the facilities are acceptable. The CPCRA program staff maintains routine contact with the investigator or study coordinator by interim site visits and phone or e-mail. To verify the accuracy and completeness of the research data, documents for trial subjects identified by the CPCRA Statistical Center are reviewed and compared with case report forms.

5. NIH Staff Involvement

The questionnaire sought to clarify the nature and extent of NIH staff involvement in the conduct of clinical trials, as well as the range of practices among the different NIH funding components. In particular, it sought to determine how staff involvement varies as a function of the particular award instrument--grant, cooperative agreement, or R&D contract, and by type--single center or multicenter.

As expected, the survey revealed that NIH staff were much more likely to take an active role in trials supported by cooperative agreements and R&D contracts than for clinical trials supported by grants. For the majority of cooperative agreements, NIH staff contributed to protocol development, recruitment, data analysis, and dissemination of results. They served as members of steering committees, monitored performance, worked closely with the DSMB, identified or selected additional participating clinics, and prepared and reviewed study publications.

NIH staff were also key in shaping R&D contracts. It was they who were responsible for establishing the goals and methods of the study and the terms of the contract. Once the project got under way, however, their role was one of supervision.

With grant-supported clinical trials, NIH staff played a minor role. The proportion with NIH staff performing various tasks ranged from a high of 41 percent to a low of 7 percent. The numbers were even lower for NIH staff involvement in clinical trials supported by program project grants (although this may well be a function of the small number of program projects--10--in the sample).

For multicenter trials, NIH staff involvement provided numerous advantages. NIH staff supplied another level of oversight. They assisted in monitoring for quality control (84%), and they helped to coordinate the diverse groups of investigators.

NIH staff also made significant and substantial contributions by arranging for appropriate FDA approvals for the use of investigational drugs or devices, and by negotiating collaborative arrangements between drug or device manufacturers and other ICs or Federal agencies. Such activities were common with cooperative agreements and contracts, but rare with grant-supported trials.

The level of staff involvement also varied greatly depending on whether the clinical trial was conducted at a single center or at multiple centers.

PERCENT OF TRIALS WITH STAFF INVOLVEMENT: SINGLE CENTER VERSUS MULTICENTER TRIALS

	Single Center	Multicenter
Range	5%-41%	43%-75%
Median	18%	64%
Mean	20%	63%
Standard Deviation	13%	11%

6. Informing Patients

The nature and adequacy of participant consent, as well as the issue of keeping subjects informed of new developments, were other important topics addressed by the survey. NIH operates on the premise that fully informed participation requires an ongoing process of communication with trial participants.

The survey revealed that the majority of clinical trials had developed standard consent materials for use across participating sites, typically with heavy reliance on "model" consent forms and commonly available brochures and videotapes. In 70 percent of multicenter trials, the study planners--trial leaders and investigators, along with NIH program staff--had developed

centralized training procedures to teach sites how to use information, recruitment, and consent materials. (For single center trials, centralized training was less pertinent.)

About half of the surveyed trials translated consent forms into more than one language, and about one fourth developed procedures for ethnically diverse communities. Some 42 percent evaluated the literacy level of the consent form.

In most clinical trials, the person presenting or obtaining consent was the PI. Less frequently it was the study coordinator or the health care provider. Community recruiters were rarely (five trials) asked to obtain consent.

In about one third of the trials, study staff contacted subjects to obtain "reconsent." This was usually done when introducing new procedures, providing new information about safety and efficacy, or extending the trial. It could not be determined from this survey if there had been times when reconsent might have been appropriate but was not obtained.

Some ICs have developed innovative strategies to ensure that consent is fully informed, and that the consent procedures are understandable and appropriate, even during lengthy or complex trials. For example, NHLBI has a number of creative approaches, including multi-component informed consent whereby the participants would consent to an initial screening and then consent is sought again for participating in the protocol. For trials involving children, obtaining continuing consent over the course of the child's developmental stages becomes an important issue.

Emerging information was usually presented to subjects informally, through the physician or other study care provider. In 23 percent of the trials, subjects were not kept informed of the trial's progress. These studies were either a) very short-term, single-contact studies, b) large-scale prevention trials where results become known only over time, or c) studies where divulging study information could have compromised masking.

In only 30 surveyed trials, the safety or efficacy information was released to the public (through public channels such as press releases or press conferences) during or at the end of the study. Twenty of these reported that the release of this information had been appropriately synchronized among study participants, health care providers, and the media.

Some studies have developed formal channels for keeping participants informed of new developments. For example, NCI's Breast Cancer Prevention Trial provides subjects with updates via a quarterly newsletter and an electronic bulletin board.

The survey also addressed the issue of recontacting subjects when new information emerges after a study has concluded. In about one third of the clinical trials, the IC or Coordinating Center had developed a plan for recontacting subjects after the

study ended. Typically this was to facilitate follow-up studies or to communicate new information relevant to the participants' health--for example, a trial involving children in a medication study, where side effects become known well after the study concludes. For the remaining trials, plans for recontacting participants had been developed by the local sites.

The survey indicated that some form of monetary reimbursement was involved in about 20 percent the trials. Some trials provided other forms of reimbursement, including travel, lodging, child care, procedures, medication, and health education classes.

7. Data Access and Publication

The questionnaire addressed four major issues: a) the need to balance patient confidentiality against the need for future notification of unanticipated risks or benefits, b) the nature and adequacy of NIH staff access to trial data, c) the implications of investigator awareness of treatment assignment and outcome data, and d) the reporting of trial results, including review procedures and public access to data.

Protecting Patient Confidentiality

NIH policy requires that research data be stored in a manner that does not directly identify individuals so that patient confidentiality can be maintained. In general, except where directly authorized by individual participants, research data that identify the participants may not be released to anyone other than individuals conducting the research and the participants.[10]

To protect patient privacy, especially for research involving mental health, including drug or alcohol use, or other types of research that involve socially sensitive traits or conditions, investigators may obtain a Certificate of Confidentiality. Issued by the Public Health Service, such a Certificate allows investigators to withhold research data that identify participants, even when requested to do so in a Federal, State, or local legal proceeding [42 CFR Part 2a, and 42 U.S.C. 241(d)].

The concept of confidentiality is often narrowly interpreted by researchers as an agreement not to identify patients by name in publications. In fact, patient confidentiality requires management strategies to make sure that individual patients cannot be identified by combining study data with information available to the public, such as birth or death records.

The responsibility for notifying subjects at some future

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[10] Institutional Review Board Guidebook, Office for Protection from Research Risks, NIH, 1993.

point about unanticipated benefits or risks is an emerging issue. Previously, collecting information that allowed long-term tracking of individual patients was viewed as antithetical to patient confidentiality. However, there is increasing recognition of the importance of new information on benefits and risks collected during post-trial follow-up. Tracking is especially difficult and costly if no provisions have been made to maintain confidential study records beyond the funding period.

Approximately 75 percent of the trials surveyed retained patient identifiers in the data set, which contained treatment assignments and outcomes. This practice transcended funding mechanisms. Patient identifiers resided either with the central data set or at the clinical site(s), and the information was usually retained beyond the funding period. Using a separate commercial repository to retain data beyond the funding period was uncommon (below 10 percent), even among multicenter studies.

Patient confidentiality is not necessarily at risk when patient identifiers are retained as part of the data set, because access to the data may be restricted. However, it cannot be assumed that all trials have such procedures in place.

Independent Data Coordinating Centers provide one way to protect masking and patient confidentiality, and to expedite future patient notification, as well. Such centers were used by 49 percent of multicenter trials and 5 percent of single center trials, and by 57 percent of trials funded by Cooperative Agreements and Contracts.

Among trials with independent data centers, centralized data entry and data entry at the sites (distributed data entry) were equally common. However, the data center's performance was monitored in just 31 percent (40 percent for cooperative agreements or contracts), primarily by the project officer.

It should be noted that limited monitoring of data centers, combined with restricted access of ICs to raw data, may adversely affect the IC's ability to monitor trials, especially multicenter trials (see below).

The Nature of NIH Staff Access to Trial Data

Public health issues often constitute the reason for permitting NIH staff access to study data. However, the IC's rights, and responsibility for monitoring trial data, are dictated by the funding mechanism. The right of Government access to grantee records is specified in Federal regulations (45 CFR Section 74.53). Government access to contractor data is described in 48 CFR Section 27.4 and is usually further spelled out in the contract.

Closely related issues are the release of study information under the Freedom of Information Act (FOIA) and protection of information under the Privacy Act. Government agency records are subject to FOIA and to the Privacy Act. Thus, if NIH takes

possession and control of trial data, the data may be subject to release under FOIA or the Privacy Act.

However, even when the Government does take possession and control of clinical trial data, not everything must be released. In accordance with the Privacy Act, patient identifiers as well as proprietary data are removed before data are released. (FOIA and Privacy Act issues are discussed in more detail in Appendix II.)

Investigators who are funded by grants and cooperative agreements retain primary rights to the data developed under the award, subject to regulations regarding Government rights to access. This right of Government access does not make the awardee's records subject to FOIA requests.

Investigators who are funded by contracts may or may not retain primary rights to the data, depending on the terms of the contract.

Public release of data under FOIA is not a trivial issue. Premature public access to trial results, particularly data presented to DSMBs, could threaten a trial's outcome and encroach upon investigators' ability to publish their results or use the data for regulatory filing (FDA[11]) by industry collaborators. Premature public access may also adversely affect public health because of the potential for misinterpretation of premature trial results. If ICs voluntarily limit their access to trial data, they may thereby limit their ability to adequately monitor the trial.

In view of the potential impact of FOIA and the Privacy Act on data access, the questionnaire asked if, and under what circumstances, the IC had requested and/or gained access to raw data. Responses suggested that approximately 45 percent of ICs did not exercise their right of **ongoing access.** Some IC staff made a practice of not accessing trial data on a routine basis, but only for important public health reasons. Some of their stated reasons were that they believed (incorrectly) that data are "owned" by the awardee, or that the IC lacked the authority to access data. An unexpected finding was that ongoing IC access to raw data was more common among masked trials (57 percent) than among unmasked trials (22 percent).

IC access to raw data **at the end of the trial** was more common (65 percent) than ongoing access, especially among multicenter trials (75 percent) and those funded by cooperative agreements and contracts (87 percent). Reasons for accessing data at the end of the trial were, in order of descending frequency (overlapping categories): Institute practice, project officer participation, funding mechanism, terms of award, upon request, other, and IND sponsor. Almost one third of the trials

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[11]FDA is involved where drugs, biologics, or devices are used.

(n=35) reported that the IC would **not** have access to data at the end of the trial because the IC obtained data only in cases of overriding public health concerns or that the IC had a policy of not requesting data. In four cases (all funded by R01 or P01), the respondents erroneously thought that the IC lacked the authority to request data.

About 40 percent of the ICs actually took possession of data tapes at the end of the trial. The practice was somewhat more common among multicenter trials (56 percent) and trials funded by cooperative agreements and contracts (66 percent).

Collaborator Access to Treatment Assignment and Outcome Data

The questionnaire inquired about access to raw data before trial's end by academic and industrial collaborators. Such collaborator access, the survey indicated, was unusual: only 19 percent of all trials (15 percent of multicenter trials and trials funded by cooperative agreement or contract) reported such access. Follow-up analysis of the positive responses made it clear that "collaborator" had been interpreted to include NIH program staff, other investigators in a center grant, and DSMB. Thus, ongoing access to data by collaborators was virtually nonexistent. This finding is consistent with that in the DSMB section indicating that interim data analysis is rarely made available to FDA or industry representatives.

Reporting Trial Results

The questionnaire asked if and by what means health care providers and the public would gain access to the raw data. It also asked if publications required prior NIH review and/or clearance.

Sixty percent of the trials had publication policies in place. Most often these had been developed by the awardee, sometimes in collaboration with the IC. Such policies were more common among multicenter trials (80 percent) and those funded by cooperative agreements and contracts (92 percent) than among single site trials or those funded by R01 or P01 mechanisms.

As expected, manuscripts were universally reviewed by the PI. They were less frequently reviewed by a publications committee (51 percent), the project officer (43 percent), the IC (28 percent), an oversight committee (22 percent), or industrial collaborators (21 percent). Multiple levels of review were more common for multicenter trials and those funded by cooperative agreements and contracts.

Institute clearance, too, was more common for multicenter trials (43 percent) and for trials funded by cooperative agreements and contracts (55 percent) than for the sample as a whole (28 percent). Institute clearance was most likely when NIH staff were among the authors.

Most of the trials provided public access to trial results

in the form of publications.

8. Computer-assisted Information Transfer

In an era marked by rapidly advancing technology, it has become clear that the flow of information in studies as complex as clinical trials cannot be fully handled manually. Computer technology has a major role to play in data collection, data stratification, data tracking, and data analysis.

A radical shift from conventional data gathering (patient charts, source documents, and hospital records) may not be well suited to all cases, especially small trials. However, multicenter clinical trials involving thousands of subjects at various geographical locations, with their great need for efficient data exchange and information dissemination, are prime candidates for computerization and electronic transfer.

Implementation of computer data management, however, presents challenges. The increasing computerization of data collection, data access, data analysis, and data dissemination introduces new dangers: loss of data, unauthorized access, data tampering, and violation of subjects' privacy. Monitoring will need to be comparably vigilant.

At present, clinical trials most commonly use computers for automated participant registration and data analysis. Such limited applications--falling far short of a "paperless clinical trial"--reflect the fact that the technology is rapidly evolving and has not yet been widely adopted by physicians and other health professionals.

Source Documents

Over 90 percent of the trials used some combination of patient clinical charts (65 percent), other paper source documents (66 percent), and computerized databases (55 percent).

Data File Security

Authorized access emerged as the most common file security system; it was used by 90 percent of samples surveyed. Log-in security was used by 52 percent; it was more customary in larger trials. Only 12 percent--primarily larger trials--resorted to encryption of data files. Very few trials (3 percent) used other security measures.

Data File Integrity

Most trials (about 95 percent) used periodic data backup to ensure data integrity. Over 50 percent performed backup daily, 40 percent weekly, and a few, monthly. Bigger trials were more likely to use daily backup than weekly backup.

Over 86 percent of the trials reported taking measures, such

as double data entry or range checks, to validate data entry.

Audit trail--which documents any modifications in data entries, and identifies who makes them--is a most desirable mechanism for protecting clinical trials data against data manipulation and tainting. The survey found that fewer than 60 percent reported some kind of audit trail. In the remaining cases, either the trials did not have it or the respondents were unaware of it.

CONCLUSIONS AND RECOMMENDATIONS

The survey revealed the breadth and diversity of NIH-supported clinical trials. Practices for managing these trials are predicated on the complexity and nature of each trial, its funding mechanism, and whether FDA or industry is involved.

For the most part, large multicenter trials supported by either **cooperative agreements** or **contracts** had multiple levels of NIH staff oversight. In **grant-supported trials**, on the other hand, oversight was uneven. This probably reflects the limited involvement of NIH staff with investigator-initiated studies.

The Committee recognizes, however, that the diverse NIH clinical trial portfolio defies formulation of any "best" policies for clinical trials monitoring. Rather, the Committee suggests that NIH consider formulating guiding principles, illustrated by examples from a spectrum of trials that have successfully accomplished similar goals.

On the basis of the survey findings, the Committee makes the following recommendations:

Random Allocation

Random allocation and unbiased outcome assessment are at the heart of valid trial results. Optimally, allocation should be accomplished in such a way that investigators and staff cannot predict and remain unaware of the allocation. One way to achieve this objective is to use a centralized system that is totally separate from the other aspects of the trial. This is accomplished in multicenter trials through a coordinating center, but single center trials do not have this facility. The Committee recommends that ICs consider supporting data service centers that would monitor entry criteria, randomize treatments and assist with outcome assessments.

Data and Safety Monitoring Boards

Most trials involving potentially harmful interventions already have DSMBs. The Committee recommends that even trials that pose little likelihood of harm, such as those introducing lifestyle changes, should also consider an external monitoring body. An external monitoring body not only assures independent assessment, it minimizes the chances of biased data collection

and ethical conflicts in cases where accumulating data suggest trends.

The sponsoring IC should appoint or approve the membership of DSMBs, with the exception of small, single center trials. The majority of DSMB voting members should be external to the study leadership and other individuals involved with the trial at hand. Besides selected NIH program staff/project officers, other key NIH staff, and trial biostatisticians, usually only voting members of the DSMB should see interim analyses of outcome data. Exceptions may be made under circumstances where there are serious adverse events, or whenever the DSMB deems it appropriate.

Quality Assurance and Site Monitoring

The survey made it clear that the implementation of a quality assurance program and the depth of the program are highly correlated with the type of clinical trial and with the funding mechanism used to support it. Most multicenter clinical trials supported by cooperative agreement or contract mechanisms employ a full array of quality assurance procedures. In contrast, single center trials supported through individual grants typically have a quality assurance program that is narrowly focused, or may have none at all.

The Committee suggests that all ICs review their clinical trial quality assurance programs and monitoring procedures to determine whether current practice(s) include, at the very least, on-site monitoring of all centers on some regular basis, as well as central monitoring of key outcome data, and a data quality program that identifies the type and quantity of data checking conducted during on-site visits.

When investigational new drugs are involved, an extra level of auditing is needed. For example, pharmacies handling investigational drugs require on-site auditing.

The monitoring and the supervision of data centers are especially critical in multicenter trials where the volume of data or the research topic(s) are especially significant for public health. Every data coordinating center should be subject to regular site visits. These should review internal operations, management procedures, data analysis, and report preparation systems.

Community Trials

By integrating research into the primary care setting, community trials have the potential to improve the transfer of research results into practice, provide critical evaluation and translation of clinical trials results, strengthen generalizations drawn from the research results (since the research cohort more closely matches the target population), enhance the training of community practitioners in clinical

research methods, and expand access to state-of-the-art therapies.

Noting these numerous advantages, the Committee recommends that NIH staff reexamine the requirements for community trials, with the goal of maximizing their potential impact and contribution. Possible areas for reevaluation include the flexibility of trial requirements (for instance, more leeway in the timing of blood draws or in meeting high tech specifications), the funding of satellites, transportation problems, and the identification of components that might not require on-site monitoring.

Level of Staff Involvement

ICs should review their policies concerning award mechanisms for Phase III clinical trials. The distinct difference in the oversight of grant-supported versus cooperative agreement or contract-supported clinical trials raises a question about what constitutes an appropriate approach to funding and oversight. Trials that require substantial NIH staff involvement mandate the use of a cooperative agreement or contract.

In determining an appropriate funding mechanism or level of NIH staff involvement, it is important to consider the characteristics of the specific clinical trial. These include the nature and complexity of the trial, its budget, and the number of participating sites, as well as the intended use of the results. It would seem prudent for trials involving potentially harmful interventions, drugs, multiple centers, or large study populations to have close NIH oversight and substantial programmatic involvement. In addition, trials (both large and small) that are of a definitive, "one-chance-only" nature and a great importance to public health also warrant substantial NIH staff attention.

The intensity of NIH staff involvement will vary from trial to trial. Some aspects of a clinical trial merit fuller staff participation than others, and it may be necessary to balance various factors against the number of staff available. It sometimes may be necessary to redirect staff from other activities to oversee certain stages of a trial. Greater attention is often required in the start-up of a trial.

Informed Consent

Multicenter trials that are broad in scope and likely to recruit from diverse populations should develop strategies that ensure appropriate informed consent across sites. The model consent form is one way to achieve uniformity and standardization, while providing sites with the flexibility to adapt the prototype to their specific needs. Consent forms need to pay close attention to issues of language, cultural factors, and level of difficulty. Steps should be taken to ensure that all participants fully understand the consent.

For some trials, the study investigators, working with the NIH staff, need to establish a process for obtaining reconsent. Guidelines should specify the points at which reconsent is appropriate.

Patient Confidentiality

NIH staff and trial investigators should identify strategies that simultaneously protect patient confidentiality and make it possible to track patients, especially for long-term trials. A good example is the NIAID-supported Pediatric Late Outcomes HIV/AIDS clinical trial. The eligible population includes infants born to HIV-infected women, children receiving antiretroviral therapy, and adolescents on treatment protocols. Participants will be followed through their twenty-first birthday.

The long-term nature of this trial means that participating sites must develop special systems to ensure both confidentiality and careful and complete tracking. It is also essential for long-term follow-up to be clearly explained in the informed consent forms.

Although a separate central data repository may be the most secure solution, such an approach may not be necessary for all trials. Depending on the size of the trial, the number of participating sites, and available funding, less stringent strategies may sometimes be appropriate.

Data Access

The Committee suggests that each IC review its policy and practices regarding IC access to trial data, in order to determine whether current practice(s) provide sufficient opportunity to monitor data while at the same time appropriately protecting the awardees' data from premature public disclosure.

With industry increasingly cosponsoring clinical trials, ongoing industry access to outcome data is another issue that deserves NIH attention. As a general practice, access to interim, unblinded outcome data should remain restricted to DSMB members. Pharmaceutical sponsors have legitimate needs for information, and should have immediate access to unblinded information on all serious adverse events, which are required by law to be reported to the FDA.

Finally, NIH staff and trial leadership should become knowledgeable about the application of FOIA and the Privacy Act to clinical trial data in various circumstances. NIH may want to consider increased training for staff who deal with clinical trials in matters of NIH rights to access data and the application of FOIA to clinical trial data, as well as privacy and future notification.

Drawing upon and sharing the experience of staff across all

ICs would be of benefit. The Committee suggests an informal seminar series or a clinical trial special interest group to fill the need for communication among NIH staff.

Computer Technologies

The nature and extent of computer-assisted support vary considerably from trial to trial. Rather than fashioning a specific model applicable to all clinical trials, it might be helpful to identify issues of data security, validation, and timeliness germane to individual trials at the time the study protocol is being developed. It might also be beneficial to make it standard operating procedure to evaluate beforehand the possible economic advantages of automating.

To broaden the use of computer technologies in clinical trials, the Committee suggests that NIH provide study sponsors with technical assistance in the form of workshops. In addition to identifying the requirements for data handling, collection, auditing, editing, processing, and storage, such workshops could assist in conducting cost:benefit studies of trial automation and in evaluating the data processing and security aspects of proposed clinical trials.

APPENDIX I

NIH WORKING COMMITTEE ON CLINICAL TRIALS MONITORING

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LINDA WRIGHT, Special Assistant to the Director, CRMC, National Institute of Child Health and Human Development

APPENDIX II

THE FREEDOM OF INFORMATION ACT AND THE PRIVACY ACT

The release of information gathered in clinical trials is regulated by two Federal laws. The Freedom of Information Act (FOIA) authorizes public access to many Government records. The Privacy Act safeguards against release of information that would infringe upon an individual's personal privacy.

Under FOIA, Government agency records are subject to release. Thus, data from clinical studies are subject to release provided that NIH has possession and control of the data.

Investigators who are funded by **grants and cooperative agreements** retain primary rights to the data developed under the award, subject to regulations regarding Government rights to access. This right of Government access does not make the awardee's records subject to FOIA requests. In Forsham v. Harris, 445 U.S. 169 (1980), the Supreme Court held that records of an NIH grantee are not records of the NIH, even though it has right of access to those records.

Investigators who are funded by **contracts** may or may not retain primary rights to the data, depending on the terms of the contract. In Burka v. HHS, Civil Action No. 92-2636 (D.D.C. December 13, 1993), the U.S. District Court for the District of Columbia held that computer tapes maintained by a National Cancer Institute (NCI) contractor were agency records because NCI had some control over the records. However, NIH does not consider this decision to govern decisions about release of other contractor records in response to a FOIA request.

Even when the Government does take possession and control of clinical trial data, not all of the data must be released under FOIA. In accord with the protections afforded by the Privacy Act, patient identifiers or other information that would constitute an unwarranted invasion of personal privacy are removed from the record before it is released. In addition, proprietary data provided by a source outside the Government, such as data collected by a university under an IND, may not be released pursuant to FOIA requests. In other words, the presence of proprietary or personal information is not a reason for withholding the entire record, but it is a reason for withholding those parts of the record containing that data.

If the Government takes possession and control of trial data, and maintains the data in records from which information can be retrieved either by the name of the individual participant or by some other identifying number, symbol, or other particular assigned to that individual, the Privacy Act applies. In such a case, to protect the identity of individual participants, the Government must establish a system of records to maintain the information, and the information cannot be released without the permission of the individual.

If information maintained in a Privacy Act system of records is requested under FOIA, only information that would be released under FOIA is made available. The agency would still remove information identifying the individual as well as proprietary information.