THE ROLE OF GENERAL CLINICAL RESEARCH CENTERS IN CLINICAL TRIALS: A CHARACTERIZATION WITH RECOMMENDATIONS

PREPARED FOR THE NATIONAL INSTITUTES OF HEALTH

MARSHA D. HOPWOOD, JOHN C. MABRY, WILLIAM L. SIBLEY

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Rand
SANTA MONICA, CA. 90406
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PREFACE

This report documents the findings of the second year of a 2-year project entitled "Evaluation of the Role of Clinical Research Centers in Clinical Trials, with Emphasis on Information Processing." This project was sponsored by the General Clinical Research Centers (GCRC) Program of the Division of Research Resources of the National Institutes of Health. The goals for the project were

- To develop a broad understanding of clinical trials, their organizational, administrative, operational, and information processing problems, and potential solutions.
- To develop a detailed understanding of the role of the GCRC Program in clinical trials, and to recommend methods for facilitating trials that make use of the resources it supports.

A companion Rand report, A First-Order Characterization of Clinical Trials, R-2653-NIH, September 1980, addresses the first of these goals.

The present report addresses the second goal. It summarizes information gathered by the authors about clinical trials that make use of GCRC Program resources and recommends changes in those resources to facilitate clinical trials. The information was obtained from structured interviews with approximately 150 clinical investigators and from informal interviews with approximately 75 support staff members. The recommendations presented are based on the interview results and their interpretation, as well as on previous Rand reports concerning GCRC Program resources and the research activities of the investigators who use them.

The information in this report should be of interest to the GCRC Program and to those who participate in its deliberations regarding future resource development and allocation. The report should also be of interest to other government, university, and private individuals involved in funding, supervising, or planning resources for clinical trials; and to information scientists and others providing resources to support clinical trials.
SUMMARY

This report describes the role of the General Clinical Research Center (GCRC) Program in clinical trials and recommends information processing methods to facilitate trials that make use of the resources it supports. It reports the results of the second year of a 2-year project entitled "Evaluation of the Role of Clinical Research Centers in Clinical Trials, with Emphasis on Information Processing."

A clinical trial is a scientific research activity in human subjects undertaken to determine, prospectively, the effect and value of preventive, diagnostic, and therapeutic agents, devices, regimens, and procedures. Trials account for a substantial portion of the GCRC Program budget and, in 1976, the President's Biomedical Research Panel recommended that the GCRCs supported by the Program be made even more widely available to clinical trials [1].

A typical GCRC is a dedicated unit with about 8 beds, 1 or more treatment rooms, a core laboratory, a metabolic kitchen, a nurses station, a conference room, administrative offices, and a patient lounge. Some centers also have outpatient areas. In addition to a principal investigator, a program director, and an advisory committee to oversee and supervise the GCRC and the research studies that use its facilities, a typical GCRC has about 12 nurses, 3 dietitians and aides, 2 laboratory technicians, an administrative coordinator, and other clerical personnel. Some GCRCs also have a minicomputer-based CLINFO [4] data management and analysis system.

To gather information with which to evaluate the role of the GCRCs in clinical trials, we conducted interviews at 19 GCRCs with 110 clinical investigators, 21 GCRC program directors, 54 support staff members, and 19 others. The investigator and program director interviews were structured, whereas the other interviews were less formal.

Interview data were supplemented by data from an earlier survey of clinical investigators who use GCRCs and their research activities [6]. Other supplementary data were taken from individual GCRC annual reports and from the GCRC directory [9]. To evaluate the adequacy of the CLINFO data management and analysis system to support clinical trials, we used additional data from data collection forms and protocols for clinical trials and from usage data collected at the first CLINFO installation. We also made use of the knowledge base we had developed during the earlier CLINFO project.

The investigators whom we interviewed were selected by GCRC program directors. The GCRCs were selected from among those that were most active in clinical trials, and the particular GCRCs visited were chosen to maximize the number of centers visited within the project budgetary constraints.

We concluded that additions to and changes in GCRC staff personnel, and additional support for investigators in statistical and information processing technologies, would facilitate the conduct of clinical trials. We also concluded that these recommendations were consistent with the objectives and budget of the GCRC Program.

The major objective of any trial is to provide valid information about an intervention relative to a particular disease and patient population. The information is usually extracted by statistical inference from carefully collected, reliable data. The recommendations made in this report outline ways of assisting investigators in attaining that objective, and suggest aids
that may improve the productivity of existing GCRC resources. Specifically, our recommendations to the GCRC program were as follows:

- Research data coordinators should be provided to support clinical trials.
- Biomedical scientists (e.g., biostatisticians and computer programmer/analysts) should be made available in the GCRCs on a regular but limited consulting basis.
- Additional capabilities should be added to the CLINFO system to facilitate information processing for clinical trials. These capabilities include analysis of covariance, improved data editing, document tracking, sample size determination, and randomization.
- A food composition analysis computer program should be provided for GCRC dietitians.
- Fiscal management and word processing computer programs should be provided for GCRC administrative coordinators.
- In addition to consulting assistance in statistics and computing, methods should be explored to help investigators increase their expertise in both fields.
ACKNOWLEDGMENTS

The authors wish to acknowledge the help of the many individuals who have contributed much of the information that underlies this report. We sincerely thank the GCRC program directors and administrative coordinators who scheduled our interviews at their institutions, answered our many questions, and showed unfailing hospitality to us during our visits. We are grateful to the many physicians, nurses, dietitians, and other research and nonresearch personnel for the information they provided and commend them for their patience and tolerance.

We would also like to thank our Rand colleagues Grace Carter, Steven Glaseman, Thomas Lincoln, and William Lisowski for their many helpful comments.
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Chapter 1

INTRODUCTION

Clinical trials are scientific research activities in human subjects undertaken to determine, prospectively, the effect and value of preventive, diagnostic, and therapeutic agents, devices, regimens, and procedures. Trials account for a substantial proportion of the funds expended by the National Institutes of Health (NIH). In 1978, the President's Biomedical Research Panel recommended that the General Clinical Research Centers (GCRCs) supported by the NIH's Division of Research Resources (DRR) be made more widely available for supporting clinical trials [1].

In response to these recommendations, and because of the level of resource support it was already providing for trials, the GCRC Program initiated a 2-year project to evaluate its role in clinical trials and to recommend an effective mix of resources that the Program could provide for trials. We began that project, "An Evaluation of the Role of Clinical Research Centers in Clinical Trials, with Emphasis on Information Processing," in September 1978. Our initial premise was that before we could make recommendations regarding support for trials that use GCRC resources, we first had to develop a broad understanding of trials and their problems in communicating and manipulating information. The first year of the project was devoted to this broad characterization, which was reported in [2]. The characterization report includes sections on terminology, quantitative descriptions (such as sample size, cost, and design parameters), organizational structures, participating professional and support personnel, and information processing functions, problems, and potential solutions.

This report covers the second year of the clinical trials project. It includes a detailed description of the role of the GCRC Program in clinical trials, as viewed by clinical investigators who make use of GCRCs' resources in these trials, and by GCRC directors and support staff. Chapter 2 describes the typical interviewed investigator, including his background and training, his sources of research support, his use of statistics and computers, his involvement in clinical trials (including problems), and resources that he would find useful to make his involvement in trials more effective and productive. Chapter 3 describes the clinical trials he conducts, including organization, design, sample size and data volume (and their impact on GCRC resources), and personnel and facility requirements. Chapter 4 examines the GCRC environment for clinical trials as viewed by the program director and support staff, including personnel and physical facilities, operational and administrative activities and problems, impact of and problems caused by clinical trials, the role of existing computer systems, and potential resources. Chapter 5 presents several models for GCRC Program support for clinical trials and, in the context of those models, recommends changes to facilitate the coordination of clinical trials, research data processing, investigator and support staff education, and GCRC management.

GCRC PROGRAM BACKGROUND

The General Clinical Research Centers Program began in 1960 as an effort to provide the resources and controlled environment necessary to perform high quality medical research
involving human subjects. From the initial 8 Clinical Research Centers and 3 million-dollar budget, the Program has evolved to support 75 GCRCs at a cost of 57 million dollars during fiscal year 1980. The objectives of the Program are "to provide an environment for studies of normal and abnormal body function, and of the cause, progression, prevention, control, and cure of human disease; to provide an optimal setting for controlled investigation by clinical scientists supported through the NIH and other organizations; to encourage increased collaboration between investigators in the basic and clinical sciences; to encourage, develop, and maintain a national corps of expert clinical investigators; and to provide a resource where advances in basic scientific knowledge may be translated into methods for improved patient care." 

A typical GCRC is a dedicated unit with about 8 beds, 1 or more treatment rooms, a core laboratory, a metabolic kitchen, a nurses station, a conference room, administrative offices, and a patient lounge. Some GCRCs also have outpatient areas and some are not discrete units, but rather contain a mixture of research and nonresearch beds. The staff for these centers are dedicated to providing support for the conduct of significant clinical research. In addition to a principal investigator, a program director, and an advisory committee to oversee and supervise the GCRC and the research studies that use its facilities, a typical GCRC has about 12 nurses, 3 dietitians and aides, 2 laboratory technicians, an administrative coordinator, and other clerical personnel.

The dedicated facilities and specially trained staff combine to make GCRCs superior to general hospital wards for the conduct of clinical research. Furthermore, some GCRCs have evolved to provide better support for specialized local clinical research interests. For example, some may have specialized laboratory and monitoring equipment.

To support the development of clinical research manpower, the GCRC Program initiated the Clinical Associate Physician (CAP) Program for postfellowship physicians. The CAP Program provides funding for young doctors to develop their skills as clinical investigators, and at the same time augments the professional staff resources at the GCRC where the CAP will conduct clinical research.

Another effort to provide support led to the development of the CLINFO data management and analysis system [4] and its installation in selected GCRCs. Other products of the DRR-sponsored CLINFO effort include a characterization of clinical researchers and other biomedical personnel and their research-related activities [5], a detailed survey of clinical investigators and their information processing activities and problems [6], and a methodology for collecting and evaluating information about the information processing activities and problems of clinical researchers.

PROJECT METHODS

The clinical trials project built on the knowledge base developed during the CLINFO project. That knowledge base included a detailed understanding of clinical research, as conducted in GCRCs, a thorough familiarity with the GCRCs and the resource support they provide, and first-hand knowledge of the objectives, design, and use of the CLINFO data management and analysis system.

The methodology for collecting and evaluating information about information processing activities and problems was also carried over from the CLINFO project. The approach used in the clinical trials project was one of iterative hypothesis formulation (clinical trials characterization, problem definition, and tentative solution generation) and hypothesis testing (solution evaluation). This approach begins with the usual review of the literature and other documents,
continues with informal interviews with appropriate clinical researchers, and ends with more formal, structured interviews. Another aspect of the methodology was to involve both information scientists and a diverse group of individuals involved in clinical trials.

SOURCES OF INFORMATION FOR THIS REPORT

Information was gathered from a variety of sources and in a variety of ways. Documents were reviewed, including articles and reports about specific clinical trials and clinical trials methodology, selected protocols, operations manuals and data collection forms, GCRC annual reports, and the NIH Inventory of Clinical Trials [7,8]. During the first year of the project, informal but semistructured interviews were conducted with about 100 individuals, including clinical trials investigators and support staff, clinical trials coordinating center personnel (data enterers, data coordinators, computer programmers, and biostatisticians), project officers, and others with responsibility for trials. This group included NIH grantees and contractors, as well as individuals from various NIH institutes, the Veterans Administration Cooperative Studies Program, the Food and Drug Administration, and pharmaceutical firms. During the second year of the project, structured interviews were conducted with about 130 people, including clinical investigators using GCRC resources in conducting clinical trials and GCRC program directors. In addition, about 75 nurses, dietitians, administrative coordinators, and other personnel were interviewed informally.

The chapters that follow provide a view of the role of GCRCs in clinical trials, point out problems, and recommend information processing solutions. Descriptions of the typical investigator, his clinical trials, the problems he encountered, his use of GCRCs, and his views about possible resources were based on structured interviews conducted with 110 investigators at 19 GCRCs. During those interviews, we requested data collection forms and protocols, which were then used to make data volume estimates for the trials described. Because investigators in GCRCs had also been interviewed in 1973 during the CLINFO project, and a few questions were common to both interviews, we compared appropriate results of the CLINFO survey [6] with the results of the clinical trials interviews. We expected that the investigators in both sets of interviews would be similar. The comparisons were made to verify that our expectation was correct and to justify the use of data obtained from the CLINFO survey and from CLINFO system use to supplement data collected during the clinical trials interviews.

Another view of the role of GCRCs in clinical trials came from structured interviews with 21 GCRC program directors. (In some locations, two physical GCRCs operate under a single grant, and we have chosen to equate a GCRC with a grant. As a consequence, we have interviewed more directors than we have counted GCRCs.) Data from these director interviews were supplemented by resource-use data from the individual GCRC annual reports and resource-availability data from the GCRC directory [9].

Informal interviews with 54 GCRC administrative coordinators, dietitians, and head nurses provided additional insight into the organization, operation, and administration of the centers. Nineteen other people were also interviewed, and these include study coordinators (e.g., research nurses who worked for specific investigators), CLINFO system managers, and Ph.D.-level biomedical scientists who provided guidance or actively participated in experimental design, equipment development, statistical analysis, and data processing.

The adequacy of the CLINFO data management and analysis system to support clinical trials that use GCRC resources was addressed by using interview data and data collection forms and protocols. These were supplemented by data from the CLINFO survey and by usage data
collected at the first CLINFO installation, the Baylor College of Medicine. The Baylor data contained such information as the number of subjects and unique data items included, and the total volume of data collected, for all clinical research studies that used the CLINFO system over a 30-month period.

In choosing which GCRCs to visit, we attempted to identify those that were particularly active in clinical trials. We did this by reviewing annual reports and by talking to program directors. Once we had a preliminary list, we chose to maximize the number of centers we could visit within the constraints of our travel budget. As a consequence, the GCRCs we visited were geographically clustered.

Based on our reading of the annual reports, we suggested the names of investigators we thought it would be useful to interview. The final selections, however, were left to the program directors.

Because neither the investigators nor the GCRCs were chosen randomly, the results of the interviews can be used to draw conclusions about the sample, but not about the entire population of centers or investigators.

Table 1.1 compares the GCRCs we visited with the total GCRC Program, based on characteristics contained in the 1978 GCRC annual reports. Although the 19 GCRCs we visited represent 25 percent of the 75 GCRCs active at the time of our interviews, they represent a higher percentage of the beds, inpatients seen, inpatient bed-days used, outpatients seen, outpatient visits, and active protocols. This is illustrated by the fact that the mean for each of those 6 characteristics is greater for the sample than for the total GCRC Program.

Table 1.1

<table>
<thead>
<tr>
<th>Selected Quantifiable Characteristics</th>
<th>Sample as a Percent of Total GCRCs</th>
<th>Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beds</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>Protocols</td>
<td>31</td>
<td>50</td>
</tr>
<tr>
<td>Inpatients</td>
<td>34</td>
<td>514</td>
</tr>
<tr>
<td>Inpatient days</td>
<td>30</td>
<td>2960</td>
</tr>
<tr>
<td>Outpatients</td>
<td>34</td>
<td>545</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>24</td>
<td>1302</td>
</tr>
<tr>
<td>GCRC sample</td>
<td>25</td>
<td>--</td>
</tr>
</tbody>
</table>

AN INFORMATION PROCESSING VIEW OF CLINICAL TRIALS

As the title of the project states, the emphasis of our work was on information processing rather than, for example, medical or ethical aspects of clinical trials. However, information processing can be interpreted narrowly, to include only computer processing of experimental data or, broadly, to look at administrative, organizational, and operational problems relating to the communication and manipulation of information. The latter interpretation would result in the consideration of aspects of project management, data management and quality control,
data analysis and reporting, document preparation, and information dissemination. We and our sponsor agreed on a broad interpretation of information processing.

From an information processing point of view, the purpose of a clinical trial is to produce information. This information may be new, or it may confirm or contradict the information produced by other trials and experiments. Following this view, the objectives of trial planning include determining what data are needed to provide the desired information (both during the course of the trial and at its completion) and establishing the mechanisms for collecting, managing, and analyzing the data. The objectives of trial start-up are to test and refine those mechanisms. The primary objective of those conducting the trial is not to treat patients, but rather to produce a data set as accurate, consistent, and complete as possible. The ongoing analysis and reporting efforts transform data into information that can be used to monitor the trial's progress and to provide an information product at its completion. This information processing view encompasses not only the capture and flow of experimental data but also the less formal flow of information among participating individuals, groups, and centers that surround the data collection effort.

This view illustrates the key role of information processing in clinical trials. It further helps to explain why individuals without training and experience in information processing may have difficulties in planning and conducting a trial. For larger, multicenter trials, the information processing expertise is often provided by coordinating center personnel and by experienced clinical investigators. For smaller, single-center trials, the responsible clinical investigator often has little or no information processing expertise upon which to draw. Often, his medical training and small clinical research studies have not provided an adequate information processing background. He typically has no staff; in particular, none with an information processing background. Consultants are often not available or are too expensive to use on a continuing basis.

The common theme of our recommendations in the final chapter is to present ideas for changes that can improve the information processing support for clinical trials that use GCRC resources. These changes may benefit trials directly or indirectly, and may involve personnel, physical facilities, computer systems, training programs, or documents, but all have the potential for improving clinical trials information processing.
Chapter 2

CHARACTERISTICS OF THE TYPICAL
CLINICAL TRIALS INVESTIGATOR

This chapter presents the results of structured interviews with clinical investigators who use GCRC resources in the conduct of clinical trials. Our characterization of the typical investigator is based on median and modal responses to a series of interview questions.

We expected that in many respects the typical investigator who uses GCRC resources for clinical trials would be similar to the typical clinical investigator interviewed for the CLINFO survey conducted in late 1973. For those questions common to both, we have compared responses obtained during the clinical trials interviews with those from the CLINFO survey.

In addition to the investigator's characteristics as a clinical researcher, we were interested in specifics about his participation in clinical trials. Thus the questions asked during the interviews went beyond those in the CLINFO survey and included clinical-trials-related questions about attitudes, level of involvement, use of computers and statistics, problems, and possible resources.

BACKGROUND AND TRAINING

The typical investigator received his M.D. in 1965 and came to the institution with which he is now affiliated in 1969. Based on the date of his degree, we can assume that the median age of the investigator is in the late 30's or early 40's. (A typical investigator in the CLINFO survey was the same age, but had come to his current institution 8 years after receiving his M.D.)

He is an endocrinologist and a full professor. Thirty percent of the investigators gave endocrinology as their specialty, compared with 34 percent in the CLINFO survey. Thirty-seven percent were full professors, 34 percent were associate professors, and 24 percent were assistant professors. This is a slight increase in seniority from the earlier survey.

He views clinical trials as his most important research activity, with other clinical investigations ranking second, laboratory (in vitro) studies third, and animal studies fourth. This should not be surprising, because investigators were selected for interviews based on prior involvement in clinical trials.

He has had little or no training in the use of computers. Seventy-eight percent had never taken a formal class in the use of computers. Twelve percent had taken one class and 6 percent had taken two classes, either as college undergraduates or as part of postdoctoral studies. Fourteen percent had some experience in writing computer programs. Only 21 percent had received any informal training. With regard to future training in the use of computers, respondents were almost equally divided between those preferring formal classes and seminars and those preferring self-study and informal instruction.

He has had some training in statistics or in designing experiments from a statistical point of view. Twenty-four percent had never taken a formal class in statistics, 40 percent had taken one class, and 13 percent had taken two. These classes were most likely (35 percent) to be part of the medical school curriculum, although classes during postdoctoral studies (29 percent)
and/or undergraduate programs (18 percent) were also mentioned. Fifty-eight percent had some informal training or self-study in statistics. With regard to future training in statistics, respondents were almost equally divided between those preferring formal classes and seminars and those preferring self-study and informal instruction.

RESEARCH SUPPORT

The typical investigator has approximately $100,000 in annual grants or contracts, but this number should be viewed with caution. Although we stressed that we were interested in research funds for which the interviewee was principal or coprincipal investigator, it was not always possible to separate training and departmental funds from research grants and contracts. Also, the dollar amount given was often described as a "rough" or "ball-park" estimate. The comparable number in the CLINFO survey was $80,000.

The typical investigator began using General Clinical Research Centers in 1973, and became aware of the GCRC at his institution informally, rather than through formal efforts to publicize it. For the 41 percent of investigators who also use other specialized clinical research centers (e.g., cancer or cardiovascular centers), the GCRC is still the prime and often only source of research beds.

Although existing GCRC resources are almost always available when he needs them, he believes that the addition or augmentation of certain resources would facilitate his research. Seventy-seven percent indicated that some change in resources would be beneficial, such as providing computers for data management and analysis; providing or improving outpatient facilities; and providing more, highly skilled support staff.

ATTITUDES TOWARD CLINICAL TRIALS

We were interested in the factors that might influence an investigator's decision about whether to become involved in a clinical trial. In addition to the scientific question to be answered by the trial and its relevance to his interests, we wondered if other scientific, administrative, or sociologic factors might influence an investigator's decision to participate.

During the first year of the project we had heard many reasons (besides those relating to scientific merit) for and against becoming involved in clinical trials. We narrowed those reasons down to 14 brief statements, and we asked the respondents to indicate the degree to which they agreed or disagreed with each statement. This exercise revealed a number of interesting and infrequently discussed factors that can influence an investigator's willingness to become involved in a clinical trial. Figure 2.1 shows the percentage of respondents who agreed or strongly agreed with each statement and the percentage of those who disagreed or strongly disagreed.

The typical investigator strongly agrees that clinical trials require a large amount of administrative and managerial effort. Because a clinical investigator in a university setting often has only a limited amount of time to devote to research, and because he often does not have sufficient funding to support an administrative staff, he may be unable to meet the administrative and managerial demands of a trial.

He agrees that in some instances multicenter trials are the only way to recruit enough subjects or widely representative subjects. A few pointed out that for certain rare diseases, there is no way to get enough subjects to do an adequate clinical trial.
Clinical trials are the only way to evaluate alternative treatments currently in use.

Clinical trials are an effective way to change medical practice.

Clinical trials are the only way to test new and promising interventions before they are put into widespread use.

Trials are a good way to get to know your peers.

Junior people have an opportunity to meet leaders in their field in trials.

Senior staff can use trials to train junior staff.

Clinical trials provide access to the treatment resources (e.g., experimental drugs) that match your interests.

Trials provide opportunities for ancillary studies that match your personal interests.

Trials require a large amount of administrative/managerial effort.

Protocol adherence, laboratory quality, and staff interest are difficult to maintain in multicenter or long-term single-center trials.

In some instances, multicenter trials are the only way to recruit enough subjects.

In some instances, multicenter trials are the only way to recruit a wide variety of subjects.

Multicenter clinical trials are often inconclusive.

Questions posed by multicenter clinical trials are important, but are not at the forefront of clinical research.

Fig. 2.1—Percentage of agreement and disagreement with statements about clinical trials
He agrees that clinical trials can provide both access to treatment resources (such as experimental drugs) and opportunities for ancillary studies that match his interests. Although few investigators disagreed, the percentage expressing strong agreement was lower than that for approximately half of the statements.

Although there was little strong disagreement with any of the statements, there was some negative reaction to a few of them. Opinion was divided on whether questions posed by multicenter clinical trials, although important, are not at the forefront of clinical research. Forty-three percent disagreed (i.e., believed that trials are at the forefront) and 52 percent agreed that trials are not at the forefront.

Some disagreement was also expressed with the statement that multicenter clinical trials are often inconclusive (33 percent disagreed, 55 percent agreed). A few who agreed commented that all clinical research is inconclusive.

Approximately 30 percent of the respondents disagreed with the statements describing trials as the only way to evaluate alternative treatments currently in use or as the only way to test new and promising interventions before they are put into widespread use. They seemed to be reacting, at least in part, to the use of the phrase "the only way," and not because of a strong conviction that there were other ways. A few commented on this directly.

INVolVEMENT IN CLINICAL TRIALS

The typical investigator has experience in designing clinical trials and in analyzing the data collected from them. Using a three-point scale of little or no experience, some experience, or considerable experience, 31 percent had some experience, and 49 percent had considerable experience in designing clinical trials. With regard to analyzing data from clinical trials, 36 percent had some experience, and 46 percent had considerable experience.

He has been involved in clinical trials both as a contributing investigator and as a study chairman. We defined a study chairman as the principal investigator for a single-center trial or the overall chairman for a multicenter trial. We defined a contributing investigator as a clinician working under the direction of the principal investigator for a single-center or multicenter trial or as the principal investigator for one site in a multicenter trial.

He has been involved in 5 single-center clinical trials, 4 of which used the GCRC. Five percent have never been involved in a single-center trial.

Funding for these single-center trials is provided by a combination of grants, contracts, and other funds. Sixty-five percent reported multiple sources of funds as opposed to a single grant or contract to provide all the necessary resources. Typically these trials are funded primarily out of a larger project, program, or center grant or contract. Fifty-two percent reported these larger grants as one common source of support. Forty percent reported that these single-center trials commonly are funded separately by sources other than NIH, e.g., by pharmaceutical firms and private foundations. Twenty-five percent reported that these trials commonly are funded separately by NIH.

The typical investigator has been involved in 1 multicenter clinical trial. Forty-three percent have never been involved in a multicenter trial. His involvement has been as part of a group organized to conduct a single trial, rather than as part of a cooperative group organized to conduct a series of trials (e.g., a cooperative oncology group).

Funding for the multicenter trial is as likely to be from a single source as from multiple sources. Forty-four percent of the respondents reported that multicenter trials commonly are funded separately by sources other than NIH, 39 percent reported separate funding by the NIH.
as a common source, and 26 percent reported funding from a larger project, program, or center grant or contract.

USE OF COMPUTERS FOR CLINICAL TRIALS

A typical investigator uses both a computer and a programmable calculator for processing clinical trials data. Forty-six percent use both, 18 percent use only a computer, and 27 percent use only a programmable calculator.

The brands and kinds of equipment used are summarized in Tables 2.1 and 2.2. Equipment manufactured by Hewlett-Packard was most often cited by respondents. We have grouped the responses to questions about the specific calculators and computers used by manufacturer into five groups:

1. *Calculators*—programmable or nonprogrammable devices that require data to be reentered for each new calculation, costing $1000 or less.
2. *Desk-top computers*—user-programmable in a language like Basic, incorporating a terminal and capabilities for storing data and programs, and costing more than $1000 but less than $10,000.
3. *Minicomputers*—user-programmable systems usually capable of supporting two or more users simultaneously, and costing from $10,000 to several hundred thousand dollars.
4. *Large-capacity computers*—multiuser systems, often called "mainframes," and costing from several hundred thousand to several million dollars.
5. *Unknown*—equipment about which insufficient information was provided.

Based on the grouping, calculators (both programmable and nonprogrammable) are most often cited as aids to processing clinical trials data.

Some interviewed investigators distinguish programmable calculators from computers by ease of use. For example, the Hewlett-Packard 9845 is a desk-top computer that some investigators classify as a programmable calculator. For them, the characteristics of both devices are probably similar; i.e., investigators can use both directly (without an intermediary), investigators need no special accounts and receive no bills, and these devices are relatively inexpensive and are conveniently located. Further, it is often easier to obtain approval to purchase a device identified as a calculator than one identified as a computer. These investigators perhaps view a computer as something that they cannot control and must use through a programmer or statistician and that is expensive and inconvenient to use.

Sixty-one percent of the investigators have grant or contract funds that may be used for computational services for clinical trials. These funds might be used to pay for computer time or to hire programmers or statisticians.

When such funds are available, a typical investigator spends $2000 per year for computational services. Fifteen percent of those with funds spend nothing, perhaps because services are not needed (e.g., data analysis is done elsewhere), services are free (such as for a CLINFO system or a departmental computer), or the available services are not usable by the investigator (because of lack of assistance or because they are too costly). Eleven percent spend between $20,000 and $200,000 per year. Investigators in this last group typically have their own computer system or make use of a substantial amount of programmer and statistician time.
Table 2.1

Brands of Data Processing Equipment Used for Clinical Trials

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Kinds of Equipment</th>
<th>Number of Times Cited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hewlett-Packard</td>
<td>Calculators</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Desk-top computers</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Minicomputers</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Texas Instruments</td>
<td>Calculators</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Digital Equipment</td>
<td>Minicomputers</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Large-capacity computers</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>IBM</td>
<td>Minicomputers</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Large-capacity computers</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Wang</td>
<td>Desk-top computers</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Minicomputers</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Data General</td>
<td>Minicomputers</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>Calculators</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Desk-top computers</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Minicomputers</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Large-capacity computers</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38</td>
</tr>
</tbody>
</table>

Table 2.2

Kinds of Data Processing Equipment Used for Clinical Trials

<table>
<thead>
<tr>
<th>Kind of Equipment</th>
<th>Number of Times Cited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculators (both programmable and nonprogrammable)</td>
<td>58</td>
</tr>
<tr>
<td>Desk-top computers (user programmable in a language like Basic)</td>
<td>23</td>
</tr>
<tr>
<td>Minicomputers</td>
<td>31</td>
</tr>
<tr>
<td>Large-capacity computers (&quot;mainframes&quot;)</td>
<td>27</td>
</tr>
<tr>
<td>Unknown</td>
<td>15</td>
</tr>
</tbody>
</table>
USE OF STATISTICS FOR CLINICAL TRIALS

The typical investigator uses the following statistical measures in analyzing clinical trials data:

- Descriptive statistics, e.g., counts, means, standard deviations (used by 97 percent of the respondents).
- T-tests (used by 95 percent).
- Linear regressions and correlations (used by 86 percent).
- Analyses of variance (used by 84 percent).
- Chi-squared tests (used by 79 percent).
- Scatter plots (used by 77 percent).
- Frequency distributions (used by 73 percent).
- Histograms (used by 71 percent).
- Other nonparametric tests, such as Spearman rank correlation and Wilcoxon signed rank test (used by 62 percent).
- Curve fitting (used by 58 percent).
- Analyses of covariance (used by 58 percent).

Of these, descriptive statistics, t-tests, linear regressions and correlations, and chi-squared tests were most often identified as being done with the aid of a programmable calculator. The remaining measures were most often identified as being done with the aid of a computer.

Only 41 percent claimed to use cross-tabulations, but this seems inconsistent with the 79 percent who use chi-squared tests. Because the chi-squared test operates on cross-tabulated data, i.e., an array of counts of values that fall in particular categories, the investigators’ responses may reflect a lack of familiarity with the term “cross-tabulations,” or “cross-tabs.”

Life table analysis is used by 28 percent of the interviewed investigators. Thirty-one percent of the investigators mentioned other statistical techniques they use, but there was no identifiable pattern to those mentioned.

IMPEDEMENTS TO CLINICAL TRIALS

We identified 52 potential activities associated with clinical trials. Interviewed investigators were asked to what extent the time required or difficulties encountered in each of those activities impede their progress in conducting a clinical trial. Responses were limited to activity not done, activity is little or no impediment, activity is some impediment, or activity is a considerable impediment. Figure 2.2 shows those activities for which at least 50 percent of the respondents reported some impediment or considerable impediment, and for which at least 20 percent of the respondents reported considerable impediment.

The activities shown in Fig. 2.2 have been identified as being considerable impediments by at least 20 percent of the investigators interviewed. All but three of these activities relate to data collection, organization, and analysis.

Responses to comparable questions from the CLINFO survey and the clinical trials interviews are shown in Table 2.3. Investigators were asked about 14 activities in the CLINFO survey, and their responses about the extent to which each activity impeded their research were limited to not at all, little, somewhat, greatly, and very greatly. It should be noted that the
Activity

Obtaining financial support.

Retrieving, reducing, and analyzing the data.

Organizing and storing the data for retrieval and analysis.

Finding all the values of a single variable for all patients.

Preparing the original proposal (e.g., organizing, writing, budgeting, and typing the proposal).

Finding all the patients with a particular characteristic or set of characteristics.

Obtaining approvals for the plan from the appropriate review groups.

Adding a new measure (variable) to all research files once the trial has started.

Filing research data for subsequent analysis.

Analyzing data to understand unanticipated events.

---

Fig. 2.2—Impediments to conducting clinical trials
Table 2.3

Comparison of CLINFO Survey and Clinical Trials Interviews for the Questions Asking the Degree to Which the Activity Impedes the Investigator's Research

<table>
<thead>
<tr>
<th>Activitya</th>
<th>Percent Citing Activity as a Great or Very Great Impediment (CLINFO Survey)</th>
<th>Percent Citing Activity as a Considerable Impediment (Clinical Trials Interviews)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain financial support.</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>Obtain approvals for research plans and protocols./Obtain approvals for the plan from the appropriate review group.</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Select and admit patients./Recruit and admit patients.</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Carry out experimental procedures and care for patients.</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Collect specimens.</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Carry out laboratory analyses.</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Organize and store data./Organize and store data for retrieval and analysis.</td>
<td>39</td>
<td>28</td>
</tr>
<tr>
<td>Retrieve, reduce, and analyze data.</td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>Write research reports to sponsor./Prepare final report on the trial outcome for your sponsor.</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Publish research papers./Prepare research papers.</td>
<td>17</td>
<td>15</td>
</tr>
</tbody>
</table>

Where two wordings are given, the first is from the CLINFO survey and the second is from the clinical trials interviews.

context for these questions in the CLINFO survey was all clinical research, whereas for the clinical trials interviews, the stated context was limited to clinical trials.

Although there are apparent differences between the percentage of investigators who were impeded in the two surveys, few of these differences are significant. A chi-squared test was performed to determine, for comparable questions, if the proportion of responses in the great and very great impediment categories in the CLINFO survey was significantly different from that in the considerable impediment category in the clinical trials interviews. There is a significant difference at the .01 level only for carrying out experimental procedures and caring for patients, and for retrieving, reducing, and analyzing data. The medical procedures used for a clinical trial must be readily repeatable for subsequent subjects, and in that sense they are not experimental when compared with the procedures for an exploratory clinical research
study. Thus the difference in responses should not be surprising. The difference in responses for the questions about data retrieval, reduction, and analysis can be explained by the inclusion in the clinical trials interviews of some investigators who typically are involved in multicenter trials. These investigators usually send completed data forms to a central data coordinating center, and are not generally responsible for data retrieval, reduction, and analysis. If we exclude these investigators, the difference in responses for the two interviews is not significant.

The 48 percent of respondents who cited obtaining financial support as a considerable impediment is similar to the 44 percent who cited it as a great or very great impediment in the CLINFO survey. Some investigators commented that obtaining support is an even greater problem than it was in 1973 when the CLINFO survey was conducted.

Organizing, storing, retrieving, reducing, and analyzing data continue to be a problem. Few of the investigators we interviewed had access to the CLINFO data management and analysis system in their GCRCs. Although computers seem to be used more frequently for data analysis than previously, data management is still difficult for most investigators.

Preparing a proposal and obtaining approvals from the appropriate review groups presented considerable impediments to about one-fourth of the interviewed investigators. Preparing proposals is often difficult, particularly for junior investigators. Although an investigator may have a good technical plan, he may not have access to the resources necessary to get a proposal budgeted, typed, and approved by his institution before it is submitted. Once a proposal is formulated, an investigator may have difficulty getting it approved by the appropriate review group. Interviewed investigators often cited repeated difficulties with institutional review boards (IRBs) and human subjects committees. Other investigators at the same institutions reported no problems at all in getting proposals approved by IRBs. The CLINFO survey found that 19 percent of interviewed investigators found that obtaining approvals for research plans and protocols was a great or very great impediment (compared with 22 percent for the similar activity described in the clinical trials interviews). No question in the CLINFO survey directly addressed the subject of preparing a proposal.

RESOURCES FOR CLINICAL TRIALS

During the first year of the project, we identified a large number of resources that might facilitate the carrying out of clinical trials. These resources include personnel, physical facilities, and documents. They include resources that we observed at one or more of the places we visited, as well as resources suggested by our experience in information processing and by our exposure to clinical research during both the CLINFO project and the clinical trials project. We then narrowed the list of resources to those that met the following criteria:

- The resources could be provided in the context of the GCRC Program and could be identified as a GCRC resource.
- The resource was technologically feasible.
- The resource was sociologically acceptable in the GCRC environment.
- The cost of the resource was compatible with the GCRC Program budget.
- The resource would be useful to many GCRC users.

The resource ideas that met these criteria were then organized into 19 examples, which we presented to the investigators we interviewed. For each resource, the investigator was asked to indicate the degree to which the resource would be useful to him, i.e., the extent to which the availability of the resource would make his participation in clinical trials more effective.
and productive. Figure 2.3 shows the percentage of respondents who thought that the resources would be very useful, useful, useless, or detrimental. (The percentage who had no opinion is not shown.)

A typical investigator thinks that the following personnel resources would be very useful in making his involvement in clinical trials more effective and productive:

- A research nurse or caseworker available to act as a data coordinator for clinical trials using the GCRC. (Sixty-nine percent thought that a coordinator would be very useful.) Such a person would support a number of different trials.
- A biostatistician available on a part-time but regular basis during the course of the trial. (Sixty-seven percent thought that this arrangement would be very useful.) This person might have other primary responsibilities, but would be available (e.g., through regular office/consulting hours) as needed by GCRC clinical trials investigators.
- A biostatistician available during the planning stages of a trial. (Sixty-six percent thought that such a person would be very useful.) This involvement might be intensive over a relatively short period of time.
- A person experienced in data form design and layout available during the planning stages. (Sixty-one percent thought that such a person would be very useful.)
- A computer scientist, programmer, and/or another person with relevant data processing skills and experience available during the planning stages of a trial. (Fifty-two percent thought that such a person would be useful.)

With regard to other resources, the typical investigator thought that several computer software systems would be very useful, namely:

- A computerized data analysis and report-generating system. (Sixty-four percent thought that this would be very useful.)
- A computerized data entry, data editing, and data retrieval system. (Sixty-three percent thought that this would be very useful.)
- A word processing system, i.e., a computerized aid for document/report preparation that would include typing, editing, and printing. (Fifty-five percent thought that such a system would be very useful.)

The strongest negative reactions were to a computerized patient-scheduling system (31 percent thought it would be useless or detrimental) and to a part-time but regularly available publications editor (29 percent thought such a person would be useless or detrimental). The negative reaction to a patient-scheduling system may reflect past unsatisfactory experience with such systems. The negative reactions to a publication editor was sometimes a result of a misconception about the role of an editor. A few investigators seemed to view an editor as a ghost writer, and stated that it would be faster for the investigator to write a paper himself than to explain all the details to an editor who would then write the paper.
Resource

A research nurse or caseworker available to act as a data coordinator for clinical trials using the GCRC.

A (part-time but regularly available) biostatistician.

Having biostatisticians available during the planning stages of a trial.

A computerized data analysis and report-generating system consistent with the data entry, editing, and retrieval system.

A computerized data entry, data editing, and data retrieval system.

Having a person experienced in data form design and layout available during the planning stages of a trial.

A computerized aid for document/report preparation that includes typing, editing, and printing (i.e., a word processing system).

Having computer scientists, programmers, and other data processing personnel available during the planning stages of a trial.

A locally available computerized system for keeping track of data collection forms and controlling errors.

A (part-time but regularly available) computer programmer.

Additional outpatient facilities.

Facilities (and personnel) available in the GCRC for training support staff for a clinical trial.

Having nurses, data coordinators, and dietitians available during the planning stages of a trial.

A computerized patient-scheduling system.

A (part-time but regularly available) publications editor.

Additional beds.

A handbook on organizing and conducting clinical trials that contains checklists, methods, etc.

A local library of manuals of operations (including data collection forms) used in other clinical trials.

Directories of investigators and titles of their active protocols in particular research areas.

Fig. 2.3—Evaluation of potential resources by investigators
Chapter 3
CHARACTERISTICS OF THE CLINICAL TRIAL
THAT USES GCRC RESOURCES

One objective of the investigator interviews was to evaluate the role of GCRCs in clinical trials in terms of what GCRC resources were used, for what purposes, and how those resources did or could alleviate the difficulties described in a companion report [2]. Toward that objective, each interviewed investigator was asked to describe in detail a trial that was representative of his involvement in clinical trials and that made use of GCRC resources. This chapter characterizes those trials based on median and modal responses to a series of questions.

Selected attributes of the clinical trials described by the interviewed investigators are summarized in Table 3.1. To the extent that the trials described are a representative sample, Table 3.1 describes the typical single-center trial and the typical multicenter trial that make use of GCRC resources.

Table 3.1

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Single-Center Trials (n = 84)</th>
<th>Multicenter Trials (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator the Chairman?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Data Coordinating Center?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Data submission frequency</td>
<td>--</td>
<td>Once/month</td>
</tr>
<tr>
<td>Number of forms per submission</td>
<td>--</td>
<td>20/month</td>
</tr>
<tr>
<td>Trial duration</td>
<td>3 years</td>
<td>2.5 years</td>
</tr>
<tr>
<td>Inpatient or outpatient?</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Sample size</td>
<td>28</td>
<td>150</td>
</tr>
<tr>
<td>Number of centers</td>
<td>--</td>
<td>8</td>
</tr>
<tr>
<td>Sample at this center</td>
<td>--</td>
<td>25</td>
</tr>
<tr>
<td>Subject accrual rate</td>
<td>2/month</td>
<td>1.5/month</td>
</tr>
<tr>
<td>Control group?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Number of groups</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Randomized?</td>
<td>(b)</td>
<td>(b)</td>
</tr>
<tr>
<td>Masked (blinded)?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Subject time on study</td>
<td>9 months</td>
<td>9 months</td>
</tr>
<tr>
<td>Inpatient days/subject</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Outpatient visits/subject</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Total outpatient visits</td>
<td>6/month</td>
<td>10/month</td>
</tr>
<tr>
<td>Detailed protocol?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Formal reports required?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Numerical data items</td>
<td>615/subject</td>
<td>970/subject</td>
</tr>
<tr>
<td>Total data volume</td>
<td>21,000 numbers</td>
<td>26,000 numbers</td>
</tr>
</tbody>
</table>

a The controls are primarily either the best available treatment or each patient acts as his own control.

b Randomized and not randomized are evenly divided.
TRIAL ORGANIZATION

Seventy-eight percent of the trials surveyed involved a single center, with the investigator acting as study chairman in 91 percent of the single-center trials and in 62 percent of the multicenter trials. The latter figure is probably somewhat high because it was not always clear whether the investigator differentiated between the activities of a central study chairman and those of an individual site principal investigator.

Of the single-center trials, 82 percent did not have a separate data coordinating center. The 18 percent (i.e., 15 trials) that did were most often sponsored by pharmaceutical firms. By contrast, 83 percent of the multicenter trials did have a separate data coordinating center. Of the remaining 17 percent, one is anomalous (involving 20 centers) and the other 3 involved only 2 centers.

For those trials that had a central data coordinating center, the median frequency for submitting data to the center was once a month, with a median of 20 forms submitted per month.

TRIAL DESIGN AND REPORTING

Operational procedures for the typical trial in our survey were documented in some way. Including both single-center and multicenter trials, 71 percent had a manual of operations, a procedures manual, or an equivalent detailed protocol. However, 88 percent did not produce formal patient safety monitoring reports. In general, patient safety is viewed as a part of patient care whether or not patients are trial subjects, and no special reporting is considered necessary.

The typical surveyed trial included a control group, was as likely to be randomized as not, and was not masked (blinded). Eighty-six percent of all the trials involved a control group, such as historical controls, current best treatment, or each subject as his own control. The median number of experimental groups was two. Overall, and in each category (single-center and multicenter), the trials were roughly evenly divided between randomized and nonrandomized. Sixty-six percent of all the trials were not masked. Of those trials that were randomized, 65 percent were also masked.

TRIAL SIZE AND POTENTIAL GCRC LOAD

The typical surveyed single-center trial involved 28 subjects. The typical multicenter trial involved 150 subjects, with 25 supplied by each participating clinical center.

Overall (with a slight increase for multicenter trials), 78 percent of the trials involved subjects as outpatients in some way. Some trials were outpatient only, and others treated subjects as both inpatients and outpatients.

A subject in a typical surveyed trial participated in the trial for 9 months, was an inpatient for 10 days, and returned as an outpatient 8 times. As the trial proceeded, 2 new patients were accrued each month. The combined visit total for all subjects in the trial was about 8 outpatient visits per month.

From the standpoint of demand for GCRC resources created by clinical trials, we found little or no difference between single-center and multicenter trials in terms of number of
subjects, inpatient days, and outpatient visits. In fact, the impact on GCRC resources of a typical surveyed trial was not substantially different from that for a typical clinical research study. The CLINFO survey showed a median sample size of 26 patients, each admitted about twice, and staying about a week for each admission.

DATA VOLUME

Data volume information from several sources is summarized in Table 3.2. We estimated the clinical trials data volumes by combining information from clinical trials data collection forms with sample sizes. The number of trials reported in Table 3.2 differs from that in Table 3.1 because not all investigators provided the data forms we requested. For purposes of comparison, we have included the data volume estimates from the CLINFO survey and derived data volumes from a study of 55 clinical research studies at Baylor College of Medicine. The Baylor data are more reliable than the others because they are taken directly from the CLINFO data management and analysis system computer files for those studies. However, they are somewhat of an overestimate because they depend on the count of CLINFO panels (data processing records) and not all the panels were completely filled in.

<table>
<thead>
<tr>
<th>Value</th>
<th>Multicenter Trials (n = 15)</th>
<th>Single-Center Trials (n = 32)</th>
<th>CLINFO Survey (n = 75)</th>
<th>Baylor Usage (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>2,550</td>
<td>896</td>
<td>900&lt;sup&gt;a&lt;/sup&gt;</td>
<td>495</td>
</tr>
<tr>
<td>Mean</td>
<td>89,956</td>
<td>81,839</td>
<td>(b)</td>
<td>11,853</td>
</tr>
<tr>
<td>Median</td>
<td>25,950</td>
<td>21,090</td>
<td>10,090</td>
<td>7,732</td>
</tr>
<tr>
<td>80th percentile</td>
<td>220,666</td>
<td>124,656</td>
<td>66,600</td>
<td>16,372</td>
</tr>
<tr>
<td>90th percentile</td>
<td>334,662</td>
<td>322,510</td>
<td>261,000</td>
<td>27,109</td>
</tr>
<tr>
<td>Maximum</td>
<td>407,038</td>
<td>478,500</td>
<td>7,500,000</td>
<td>95,634</td>
</tr>
</tbody>
</table>

<sup>a</sup>Ten percent of the studies included in the CLINFO survey collected 900 or fewer items of data in the course of the study.

<sup>b</sup>Data not available.

A data base for a typical surveyed trial contains approximately 25,000 numbers, with little real difference between a typical single-center trial and a typical multicenter trial. The clinical trials values correspond closely with the CLINFO survey estimates. In the sense that the Baylor data represent actual counts rather than estimates, the clinical trials data volume numbers are probably overestimates in the same way that the CLINFO survey numbers were overestimates. The CLINFO system was designed to meet the needs of 80 percent of the GCRC
studies, based on the survey overestimates combined with data from other sources. Because the clinical trials numbers approximate the CLINFO estimates, it is likely that the CLINFO system could accommodate the data volume requirements of at least 80 percent of the clinical trials that use GCRC resources.

REQUIRED PERSONNEL AND FACILITIES

In the course of describing a specific trial, each investigator was asked to identify the facilities and personnel required for the trial, and to indicate their sources. In particular, each was asked to what extent GCRC facilities and personnel satisfied those requirements. Tables 3.3 and 3.4 show, for each resource, the percentage of trials for which the GCRC was the only source, for which both the GCRC and other sources were used, for which other sources were always used, and for which the resource was not needed. Note that each trial used GCRC resources in some way.

Research beds and specialized inpatient nursing care are the most important resources that a GCRC provides for clinical trials. We found that these inpatient research resources were rarely available from another source.

The use that trials made of the GCRC dietitian and diet kitchen depended on available facilities. Some GCRC kitchens provided all meals for GCRC inpatients. Others provided only research diets and some therapeutic diets, with the routine meals provided by the hospital food service. Trial subjects frequently received routine house diets or therapeutic diets while they were inpatients, and only occasionally were true research diets required. Further, GCRC kitchens did not have adequate capacity to provide meals to large numbers of trial outpatients.

Although investigators used the GCRC core laboratories, they also tended to use their own or other research laboratories for specialized determinations and to use hospital laboratories for routine determinations.

A typical surveyed trial could not meet its needs for computer systems and calculators with GCRC resources. It is reasonable to expect investigators to provide their own calculators but not their own computer systems. A common and widespread requirement for computerized data

| Table 3.3 |
| Resources Supplied by GCRC and Other Sources |

<table>
<thead>
<tr>
<th>Resource</th>
<th>Percent of Trials for Which Resource Was Supplied by--</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GCRC</td>
</tr>
<tr>
<td>Beds</td>
<td>70</td>
</tr>
<tr>
<td>Laboratories</td>
<td>6</td>
</tr>
<tr>
<td>Outpatient areas</td>
<td>31</td>
</tr>
<tr>
<td>Diet kitchen</td>
<td>49</td>
</tr>
<tr>
<td>Computers/calculators</td>
<td>3</td>
</tr>
</tbody>
</table>
### Table 3.4

**Personnel Supplied by GCRC and Other Sources**

<table>
<thead>
<tr>
<th>Type of Personnel</th>
<th>Percent of Trials for Which Personnel Was Supplied by--</th>
<th>GCRC</th>
<th>Other</th>
<th>Not Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurses</td>
<td>46</td>
<td>49</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Ward clerks</td>
<td>67</td>
<td>14</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Caseworkers</td>
<td>6</td>
<td>3</td>
<td>32</td>
<td>59</td>
</tr>
<tr>
<td>Data clerks</td>
<td>1</td>
<td>6</td>
<td>59</td>
<td>34</td>
</tr>
<tr>
<td>Dietitians</td>
<td>50</td>
<td>6</td>
<td>5</td>
<td>39</td>
</tr>
<tr>
<td>Technicians</td>
<td>8</td>
<td>30</td>
<td>59</td>
<td>3</td>
</tr>
<tr>
<td>Secretaries</td>
<td>3</td>
<td>13</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>Statisticians</td>
<td>0</td>
<td>4</td>
<td>76</td>
<td>20</td>
</tr>
<tr>
<td>Coordinators</td>
<td>20</td>
<td>15</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Programmers</td>
<td>3</td>
<td>2</td>
<td>61</td>
<td>34</td>
</tr>
<tr>
<td>Biomedical scientists</td>
<td>1</td>
<td>5</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Management specialists</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Junior physicians</td>
<td>1</td>
<td>2</td>
<td>84</td>
<td>13</td>
</tr>
<tr>
<td>Senior physicians</td>
<td>1</td>
<td>10</td>
<td>84</td>
<td>5</td>
</tr>
</tbody>
</table>

Management and analysis support for clinical research was established by the CLINFO survey [6], and the argument for such support is even more compelling for clinical trials.

The GCRC also failed to satisfy the personnel needs of a typical trial with respect to data clerks, technicians, secretaries, statisticians, programmers, junior staff physicians, and senior staff physicians. Of course, there is no requirement for the GCRC program to meet all the needs of clinical trials, and it may even be undesirable to do so. The investigator or his department should be responsible for providing nonresearch clerical support. Funding a staff dedicated to supporting the work of a single investigator should be the responsibility of the investigator, and not of the GCRC.

The need for changes in resource support has already been recognized by the GCRC Program and is being addressed. Many of these changes favorably impact support for clinical trials as well as other clinical research. For example, one result of the Clinical Associate Physician (CAP) Program is to provide additional professional resources to the GCRCs at which CAP positions are funded. The installation of CLINFO data management and analysis systems at selected GCRCs is continuing. The CLINFO system manager and other related personnel also provide statistical and programming capabilities. However, the rate at which the CLINFO system (as well as other resources) becomes available to the individual GCRCs is very sensitive to budget considerations. In the interim, there is a need for closer working relationships between the investigators and the statisticians and information processing personnel in the research community.
PERSONNEL INVOLVEMENT DURING PARTICULAR TRIAL STAGES

In addition to exploring the sources for personnel for a particular trial, we asked about the kinds of personnel most likely to participate in each stage of that trial. The percentage of trials that involved personnel of a particular category during each stage is shown in Table 3.5.

Table 3.5

<table>
<thead>
<tr>
<th>Type of Personnel (n = 109)</th>
<th>Percent Involved in Trial Stages$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Yourself</td>
<td>96</td>
</tr>
<tr>
<td>Senior staff</td>
<td>58</td>
</tr>
<tr>
<td>Junior staff</td>
<td>28</td>
</tr>
<tr>
<td>Nurses</td>
<td>11</td>
</tr>
<tr>
<td>Dietitians</td>
<td>7</td>
</tr>
<tr>
<td>Caseworkers</td>
<td>2</td>
</tr>
<tr>
<td>Technicians</td>
<td>16</td>
</tr>
<tr>
<td>Secretaries</td>
<td>29</td>
</tr>
<tr>
<td>Other institutions</td>
<td>39</td>
</tr>
<tr>
<td>Biomedical scientists</td>
<td>17</td>
</tr>
<tr>
<td>Management specialists</td>
<td>1</td>
</tr>
<tr>
<td>Statisticians</td>
<td>28</td>
</tr>
<tr>
<td>Computer scientists</td>
<td>10</td>
</tr>
<tr>
<td>Programmers</td>
<td>5</td>
</tr>
</tbody>
</table>

$^a$Trial stages: I = Initiation, P = Planning, S = Startup, C = Conduct, A = Analysis

It is not surprising that the investigator and other physicians are heavily involved in all stages of a trial. The junior staff (e.g., research fellows and residents) participate in all stages, their largest contribution occurring during the actual conduct of the trial. Neither is it surprising that the nonphysician medical staff contribute primarily during trial start-up and conduct. The relatively low percentage of trials that involve the support staff in planning is consistent with many of the comments made during interviews with support staff members. From those interviews it became apparent that support staff would feel much more a part of a trial if they were involved earlier and could contribute as well as advise the trial planners in areas affecting staff work. Personnel from other institutions are usually involved in pharmaceutical manufacturer-sponsored trials. Other biomedical scientists are used as consultants throughout a trial. The trials are sufficiently small that there is no investigator-perceived need for specialists in management techniques.

The percentages for statistician-use in trials bear out a common observation by statisticians that their first contact with investigators often occurs when they are presented with the
data from a completed experiment for analysis. Roughly a third of the trials avail themselves of statistical advice during the planning stages and about half make use of statisticians in some way. There does not seem to be any relationship with other investigator characteristics that would help to explain the lack of involvement by statisticians. Such items as experience (years since M.D.), formal exposure to statistics, trial size, multicenter versus single-center trials, and proximity to resources (although the trials in some GCRCs did tend to have more statistical help) did not relate to the use or nonuse of statisticians. The explanation may have been given by interviewed investigators who remarked about the difficulty of establishing a good working relationship with a statistician and finding one who is sensitive to the difficulties arising from clinical investigation as opposed to those incurred in laboratory or epidemiology studies.

STAFF STABILITY AND CONTINUITY

To determine the adequacy of personnel resources for trials, we asked several questions about personnel requirements, hiring, and retention. We were particularly interested in the problems of maintaining a trained staff across funding cycles. Table 3.6 shows, for a number of personnel categories, the percentages of trials for which more people were needed, new people were hired at the start of the trial, new people were hired during the course of the trial, or investigators desired to retain people at the completion of the trial but lacked the funding to do so.

Table 3.6

<table>
<thead>
<tr>
<th>Type of Personnel</th>
<th>Percent of Trials Requiring--</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More People</td>
</tr>
<tr>
<td>Senior staff</td>
<td>7</td>
</tr>
<tr>
<td>Junior staff</td>
<td>29</td>
</tr>
<tr>
<td>Nurses</td>
<td>23</td>
</tr>
<tr>
<td>Dietitians</td>
<td>9</td>
</tr>
<tr>
<td>Caseworkers</td>
<td>8</td>
</tr>
<tr>
<td>Technicians</td>
<td>34</td>
</tr>
<tr>
<td>Secretaries</td>
<td>21</td>
</tr>
<tr>
<td>Biomedical scientists</td>
<td>9</td>
</tr>
<tr>
<td>Management specialists</td>
<td>1</td>
</tr>
<tr>
<td>Statisticians</td>
<td>18</td>
</tr>
<tr>
<td>Computer scientists</td>
<td>19</td>
</tr>
<tr>
<td>Programmers</td>
<td>21</td>
</tr>
<tr>
<td>None of the above</td>
<td>24</td>
</tr>
</tbody>
</table>

*These were people that investigators wanted to retain at the trial’s completion but lacked funds to do so.
The typical surveyed trial is understaffed, and new personnel may or may not be hired at the beginning or during the course of the trial. Seventy-six percent of the surveyed trials needed additional personnel. The need for additional nurses, technicians, and secretaries may in part be a need for a general purpose assistant rather than an individual with very specific skills. Investigators who had such assistants typically identified them as technicians or research nurses. The most often mentioned requirement was for a technician, and this person typically would have a wide range of responsibilities (e.g., data collection and presentation, patient scheduling, drawing blood, and limited clerical activities). Meeting the need for statisticians and personnel with computer-related skills is made difficult by communication problems, i.e., a lack of appreciation by both the investigators and the needed personnel of the requirements of each others' disciplines.

Few new people are hired specifically for clinical trials that use GCRCs because the investigators typically lack funds to do so. Instead, they make use of people already in the environment by changing some of their responsibilities, which are changed again when the trials end. Unfortunately, these changes sometimes fragment staff personnel time or result in conflicting responsibilities, thus making it difficult for them to provide the level of support needed by trials.

PERSONAL WORKLOAD

Investigators' estimates of how their personal workloads for particular trials differed from those for other research projects are shown in Table 3.7.

Approximately one-half (49 percent) of the investigators who described single-center trials thought they created more or considerably more workload than multcenter trials. Thirty-eight percent of the investigators who described multcenter trials thought that they caused more or considerably more work. The difference might be attributable to the fact that for multcenter trials the individual investigator was not responsible for data management and analysis, but for single-center trials, he bore the whole burden.

Table 3.7

<table>
<thead>
<tr>
<th>Estimate That Workload for Trial Is--</th>
<th>Percent of Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single-Center (n = 86)</td>
</tr>
<tr>
<td>Considerably less</td>
<td>7</td>
</tr>
<tr>
<td>Less</td>
<td>14</td>
</tr>
<tr>
<td>About the same</td>
<td>30</td>
</tr>
<tr>
<td>More</td>
<td>27</td>
</tr>
<tr>
<td>Considerably more</td>
<td>22</td>
</tr>
</tbody>
</table>
Chapter 4
CHARACTERISTICS OF THE GCRC ENVIRONMENT

To provide other views of the role of GCRCs in clinical trials, we conducted structured interviews with GCRC program directors and informal interviews with other people in the GCRC environment. Some of our questions dealt with GCRC resources for all clinical research, and others specifically addressed the impact of clinical trials. Because the CLINFO data management and analysis system will be available in an increasing number of GCRCs over the next few years, we also assessed its potential to provide support for clinical trials.

THE DIRECTOR’S VIEW

We interviewed 21 GCRC program directors to determine their assessment of the resources available to them and the feasibility and desirability of making those resources more widely available for clinical trials. The characterizations of the typical GCRC and typical GCRC director that follow are based on median and modal responses to a series of questions.

Personnel Resources

The typical GCRC director has held his current position for 6 years. The number of years ranged from less than 1 to 18.

The GCRC staff typically includes 11 nurses, 1 ward clerk, 1 research dietitian plus aides, 2 laboratory technicians, 1 administrative coordinator, and a half-time secretary, but no caseworkers or data clerks. The range of the number of nurses was wide, varying from 3 to 32. Only 4 of the centers had any caseworker positions, and only 3 had data clerks.

All the surveyed GCRCs had at least fractional funding for 1 senior medical staff member (the program director), and some had as many as 2.2 positions. Although 15 centers had no junior staff, 5 had one funded position (usually a clinical associate physician). Seven centers had at least partial funding for a biomedical scientist, and 6 had some funding for a computer scientist or programmer. None of the surveyed centers reported funding for management specialists or statisticians.

Personnel Turnover

As seen by the program director, personnel turnover in the typical GCRC is not a problem. The typical head nurse and research dietitian have been in the GCRC for many years. The only personnel category for which turnover presents any problem at all is nursing. The typical response described nursing staff turnover as a slight problem, with one-third of the directors rating nursing staff turnover as a moderate or great problem. The GCRC nursing turnover rate is much lower than that for the hospital as a whole.

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Facility Resources

The typical GCRC has 8 beds, 1 outpatient area, 1 laboratory, and 1 diet kitchen. The number of funded beds ranged from 3 to 22. Over half of the centers had 1 outpatient area, 5 had more than 1 (as many as 9), and 5 had none. Five GCRCs had no laboratory, and 4 had no diet kitchen.

The typical GCRC has no computers or computer terminals, but does have 1 or more calculators. Five GCRCs had a computer system (3 of these were CLINFO sites) and 6 had 1 or more computer terminals.

GCRC Inservice Training

Approximately one-half of the GCRCs surveyed provide inservice training for support staff. This training is usually informal and includes lectures and seminars from investigators using the GCRC (sometimes regarding specific protocols), seminars held by the hospital nursing service, and outside classes. Training is often specific. Examples are seminars devoted to explanations of specific protocols or of new GCRC nursing procedures. More general training includes programs run by the hospital nursing service so that nurses can be certified to carry out new procedures or to use new equipment.

The amount and kinds of training provided depend on the kinds of protocols that are active and how often substantially new protocols are introduced, the rate of nursing turnover, and the extent to which nurses not part of the regular GCRC staff are used.

Training for Specific Protocols

An important activity that must be completed before any clinical research protocol can be activated in a GCRC involves the formulation of specific study procedures and the instruction of the nursing staff about those procedures. Formulation of procedures requires close cooperation between the investigator and appropriate support staff members (typically the head nurse and dietitian). The specific procedures are usually recorded in a notebook that remains in the GCRC for the course of the study. The investigator or head nurse may present the study and its required procedures at a regularly scheduled meeting of the nursing staff or at a meeting organized specifically for the study. Alternatively, the head nurse may inform staff members individually.

GCRC Protocol Review

Review and approval of protocols to use GCRC facilities are carried out by the GCRC Advisory Committee. The protocols may be circulated among the committee members before they meet; occasionally, a formal meeting is not required. Nurses, dietitians, and administrative coordinators may be consulted as to the feasibility of the study in terms of scheduling or patient load; support staff members attend the Advisory Committee meetings in 75 percent of the GCRCs we visited. Approval of the protocol by the Human Subjects Committee (or its equivalent) usually takes place before the review by the GCRC Advisory Committee.
Computer Support of GCRC Operational Activities

GCRC program directors think that computers would be useful for supporting operational activities. Ninety to 95 percent of the directors thought a computer would be useful for recording and reporting usage statistics and preparing reports and papers, although only 25 percent of the centers used a computer to perform those tasks. Seventy-one percent of those directors whose GCRCs had diet kitchens thought that a computer would be useful for planning diets, but only 21 percent said computers were so used. Two-thirds of the directors whose GCRCs had core laboratories believed that a computer would be useful for maintaining quality control in laboratory analyses, but only 20 percent used computers toward that end. Ninety-four percent of those handling laboratory data stated that a computer would be useful for reducing and transforming laboratory data, but only 41 percent reported that a computer was now used for that purpose. This activity—handling laboratory data—represented the most common use of computers among the directors we interviewed.

Other activities such as keeping inventory records current and preparing GCRC budgets were thought to be appropriate functions for a computer by slightly more than half of the directors, although few actually use a computer for those purposes. Only one function—the scheduling of staff, facilities, and patients—was thought not to be appropriate for computerization by most (70 percent) of the directors. (Scheduling of beds is usually done by the head nurse or the administrative coordinator.) Eighty percent of the directors we spoke to were aware of the capabilities of a word processing system. Once the nature of such a system was explained to the directors, 90 percent thought that it would be useful.

Advertising GCRC Resources

Twelve of the 21 directors interviewed had printed materials available that described the GCRC, and 9 directors conducted introduction or orientation seminars for potential users of the center. A variety of methods were used by the directors to advertise the existence and scope of available resources of the GCRC: memos or presentations to departmental meetings; rotation of residents and other staff through the GCRC for a month or longer; personal contact with new or potential users; and reliance upon members of the local GCRC Advisory Committee to contact investigators within their own departments.

Use of GCRC Resources by Clinical Trials

A typical surveyed center had 15 active trials concurrently using its facilities, with a range of 6 to 50 trials. Approximately one-half of the available resources in a typical surveyed GCRC were used to support clinical trials. The resources included those facilities and personnel that all centers had, such as beds and nurses, as well as resources not available in all GCRCs, such as outpatient facilities, laboratories, dietitians, and caseworkers.

Clinical trials typically use GCRC resources while performing baseline evaluations, administering initial treatment, and providing inpatient care and examinations. Outpatient care and examinations use GCRC facilities less often, primarily because GCRCs typically are not well equipped to support outpatient research. Trials infrequently use GCRC resources for patient eligibility determination, dose calibration, patient education, or data analysis.
Problems Caused by Clinical Trials

Clinical trials create problems for the GCRC directors in terms of ethics, resource allocation, and funding renewal. Several of the directors we spoke to expressed concern about allowing the GCRC to be used for drug trials sponsored by pharmaceutical firms, fearing that this provided NIH support for a profitable venture or that such trials were redundant and had little scientific merit. Further, independent of the source of funding or intervention under study, clinical trials typically received low marks from GCRC site reviewers.

When asked about specific problems caused by trials, 75 percent of the directors interviewed indicated that they needed a caseworker to collect data or teach subjects during outpatient visits. Of those directors who said that they needed such a person, less than half had one available.

Resources To Facilitate Trials in the GCRC

The typical interviewed director believed that trials would be facilitated if his center had more or improved outpatient facilities and improved computational resources. Other resources also mentioned by some directors were more beds and bed-space flexibility and more laboratory technicians, social workers, and data collectors.

VIEWS EXPRESSED BY OTHER GCRC STAFF

Informal interviews were conducted with 18 administrative coordinators, 16 dietitians, and 20 head nurses, all of whom were GCRC staff members. Nineteen other people, including 6 study coordinators, 5 physicians, 4 biomedical scientists, and 3 CLINFO system managers were also interviewed. Of these 19, 4 study coordinators, 1 physician, 1 biomedical scientist, and all 3 system managers were supported with GCRC funds.

These interviews were intended to explore operational and administrative problems from a different perspective than that provided by investigators and directors. Because many different topics were covered, the results of interviews with support staff are presented as a summary of problems and possible solutions, rather than as median or modal responses to questions.

Views Common to Different Categories of Staff Personnel

A general theme of the comments made by administrative coordinators, dietitians, and head nurses is that they believe they could do a more effective job if they were provided with information about a new protocol well in advance of its activation. One way to obtain some of this information is through involvement in the protocol review process, an approach generally favored by the support staff. Although support staff members from 75 percent of the GCRCs we visited attend the local advisory committee meetings, staff members at the rest of the centers are excluded. Further, at those centers where support staff members do attend, the coordinator is almost always involved but the head nurse or dietitian may not be. Even when staff attend these meetings, they sometimes do not receive adequate information about the impact of specific protocols on the resources they provide. Active involvement before a protocol is approved provides the opportunity for key support staff members to point out instances in which the protocol requires support they cannot provide; e.g., the protocol requires the GCRC
nurses to take actions for which they lack certification or requires the dietary staff to provide more special meals than is feasible given available resources. Involvement before a protocol is activated helps to familiarize the staff with protocol requirements and provides information for planning the use of nursing and dietary resources, as well as physical facilities.

Many commented on the lack of established standards and procedures. Some cited the lack of consistency in nursing and dietary procedures. Others commented on the need for a handbook describing administrative procedures. Still others described the need for written guidelines for investigators to clarify the investigators' responsibilities in carrying out a protocol using the GCRC.

Lack of performance feedback was a problem often cited by the support staff. The head nurse provides performance reviews for the nursing staff, and the dietitian for the dietary staff, but the senior support staff often do not receive reviews of their own performance. This problem can be particularly acute for administrative coordinators and dietitians, who often have no peer group in the institution. Regional and national meetings for GCRC support staff have provided a mechanism for informal review and sharing of experience, but often the local GCRC does not provide support for staff to attend.

The Administrative Coordinator's View

A major portion of the coordinator's time is devoted to two activities: annual report preparation and fiscal management. The annual report typically takes 1 month of full-time effort to prepare. Data on resource use, income, and expenses must be tabulated. This is often complicated by inaccuracies and delays in the hospital accounting system. Accomplishments of the GCRC must be compiled, and some investigators may have to be cajoled or threatened before they provide the necessary information. Because reporting requirements may change from year to year, the required information may not have been collected during the year, and thus the coordinator may have to derive the needed information. Finally, before the final version is completed, the annual report may have to be typed and retyped several times.

The largest portion of a coordinator's time goes into fiscal management. Fiscal management is necessary both for effective use of GCRC resources and for reporting purposes. Typically, the coordinator manually maintains ledgers to record all expenses charged to the grant and all income received from nonresearch use of facilities. Hospital billing and accounting systems often produce inaccurate information, and thus the manual records are needed as backup. Moreover, hospital systems sometimes cannot provide information in a timely fashion, and thus a coordinator must rely on other (usually manual) methods to track GCRC expenditures.

Typically, a coordinator must develop her own procedures for GCRC fiscal management. Coordinators from different GCRCs have shared ideas with each other at national and regional meetings. Some coordinators have worked together in an effort to produce a handbook to provide guidance for new coordinators.

The Nurse's View

The head nurses stated that they were most effective in those instances when they clearly understood the research protocol and its objectives. They would like investigators to conduct inservice familiarization sessions for the nursing staff before activating protocols significantly different from those previously used in the GCRC. They would like to know the details of what they are to do and have some sense of why it is to be done. They would also like to have
occasional inservice sessions at which investigators present the significant outcomes of their clinical research.

A problem cited by nurses is that they are given responsibility without authority. They would like investigators to be better informed about investigator responsibilities in conducting a clinical research study. Investigators tend to overlook the limits to actions that nurses can legally take. They sometimes avoid getting informed consent in a timely fashion and the nursing staff may be assigned responsibility for seeing that consent is obtained. Because protocol specifications are sometimes incomplete and because investigators sometimes do not communicate with the nursing staff in advance of protocol activation, nurses may have problems in translating general protocols into specific nursing procedures.

Nurses have developed protocol and procedure handbooks as aids in carrying out clinical research. At some GCRCs, the nursing staff develops and maintains a notebook for each active protocol. A notebook typically includes the written protocol, specific instructions and detailed schedules, sample forms, names of people to contact if questions or problems arise, and some information about each subject who has been seen under the protocol. Standard procedures notebooks typically contain detailed descriptions of nursing procedures used at that GCRC. Both of these aids help to maintain quality and consistency across nursing shifts and over the course of a study. They are particularly useful when subjects for a particular protocol are admitted infrequently or when there is turnover in the nursing staff.

The Dietitian's View

The dietitians we interviewed spend a large part of their time doing repetitive calculations with the aid of a simple calculator. Such calculations typically involve searching nutritional composition tables, transcribing values, and calculating the amount of various nutrients in a particular diet. These calculations may be done in preparing special or balance diets, in determining composition of food returned or waste materials, or in analyzing information from diet histories. Although computer programs are available that would eliminate most of the manual search, transcription, and calculation, dietitians believe that they are too expensive to use.

Many dietitians are interested in carrying out dietary research and have done so as part of studies done by physicians using the GCRC. Some have become involved with research in other hospital units. Independent funding is difficult for the dietitians to obtain.

The nature of the job of the research dietitian in a GCRC has changed over the years. Fewer metabolic and highly specialized diets are required, partly because of changing technology and investigator interest and knowledge. Dietitians must often provide their own direction.

CLINFO AND CLINICAL TRIALS

Because the CLINFO data management and analysis system will be available in an increasing number of GCRCs over the next few years, it has the potential to be used for managing data from many clinical trials that use GCRC resources. With that in mind, we thought it important to assess the adequacy of the system to support the kinds of trials described by the investigators we interviewed. Two aspects of that assessment were system capacity and system functionality. Capacity issues include the number of subjects and data volume of individual trials and how those relate to system limits, and the impact of the data
processing load created by trials on the system's availability and responsiveness. Functionality issues include the appropriateness of existing system capabilities. As a result of the assessment, we have noted a number of system enhancements that would facilitate clinical trials.

System Capacity

Chapter 3 presented a characterization of trials that use GCRC resources. It included a discussion of the number of subjects and the data volumes for single-center and multicenter clinical trials described by investigators, and for clinical research studies that used the CLINFO system at the Baylor College of Medicine. Figure 4.1 presents the cumulative percentages of studies with given sample sizes for single-center trials, multicenter trials, and the Baylor CLINFO studies, respectively. Figure 4.2 presents similar information about data volumes. The comparison of the trial data estimates with the Baylor data leads to the conclusion that trials, especially the multicenter ones, tend to collect more data and have larger sample sizes than the typical mix of clinical research studies conducted in a GCRC.

The larger sample sizes and data volumes for clinical trials described by investigators do not exceed the limits of the CLINFO data management and analysis system. The latest version of that system will easily accommodate the sample sizes thus far encountered in the GCRC environment; up to 5488 subjects can be included in an individual study data base. (The prototype system limit of 392 subjects per study accommodates 98 percent of the single-center trials and 79 percent of the multicenter trials.) Nor is data volume a problem. Eighty percent of all the trials surveyed collected no more than about 180,000 numeric items over the life of the study. Allowing 4 characters per number (sufficient space to contain a number with 6 significant digits in scientific notation) and 100-percent overhead for data base management, the space required for an 80th percentile trial is about 1.5 million characters. The space available on the CLINFO systems already includes, or can be easily extended to include, provision for 50 to 100 million characters.

Even though 5488 subjects can be included in a data base, the task of analyzing the data for trials with sample sizes greater than 799 subjects can be a problem. CLINFO data analysis procedures operate on rectangular arrays of data ("worksheets") that can have at most 799 rows and columns. The procedures expect that all the data to be analyzed or compared will be arranged in columns (or rows) but that the data will not continue from the end of one column to the top of another. Thus the effective number of patients whose data can be analyzed simultaneously is 799. Fortunately, 799 rows is enough space to accommodate the sample size of 99 percent of the single-center trials and 88 percent of the multicenter trials described by interviewed investigators.

Another potential problem lies in the impact that data management and analysis activities for a clinical trial would have on the general responsiveness and availability of the system. One would expect the processing load to increase linearly with the amount of data to be processed (excluding such time-consuming procedures as sorting). Interactive systems such as CLINFO depend on the inactivity of some of their users at any given moment ("think time") to provide the kind of responsiveness that is conducive to interactive problem solving. As the data processing for any study tends to fill all of that study's allotted time (its "time-slices") and thus not give the impression of "thinking," the responsiveness of the system degrades to the point of seriously impairing its usefulness to other less-demanding studies. Thus, even though the existing CLINFO systems have the potential capacity for handling the data management and
Fig. 4.1—Cumulative percentage versus log of sample size

Fig. 4.2—Cumulative percentage versus log of data volume
analysis for the trials we have examined, a few large trials or other studies should not be allowed to dominate the system and drive out many smaller studies.

The question of whether the data generated within a GCRC can be reasonably entered via a CLINFO terminal without dominating both the system’s terminals and a data enterer’s time (if that person is a GCRC employee with other responsibilities) must also be considered. If we take the model of a 16-bed GCRC with half of its beds devoted to trials, and with each trial generating about 20 outpatient visits a month (the 80th percentile level), on the average there will be 16 patient contacts a day. The assumptions are that there are 8 simultaneous trials, each with 1 inpatient and each generating 1 outpatient visit a day. At the 80th percentile level, each patient contact generates 170 items of information. Thus, each GCRC day generates 2720 items. An experimental data entry session showed that it takes about 15 minutes to enter 200 data items, including some time for paper shuffling. If one allows another 15 minutes for checking the correctness of the entries, the result is about 7 hours, or the equivalent of 1 person and 1 computer terminal per day to do data entry. The same model using median values (i.e., 4 beds devoted to trials, 4 outpatient contacts per day, and 75 items per contact) gives a value of 1.5 hours per day. The first set of assumptions is a patent overestimate, but is still within reason. The second set results in almost no additional load. Of course, such things as outpatient clinics can create peaks in the data entry workload, but those peaks average out over time.

The capacity of the CLINFO data management and analysis system seems adequate to support the computing requirements of the clinical trials that now make use of GCRC resources. The sample size and data volume estimates for these clinical trials put them individually and collectively within the capacity of the CLINFO system. The impact of these trials on system performance may be a problem, but only if a few large trials are allowed to dominate.

System Functionality

The CLINFO data base organization and its data management procedures were derived in part from the TOD system [10]. TOD was designed primarily for recording data from patient visits and is thus well suited to clinical trials. The CLINFO data base is also organized by patient, allowing for multiple occurrences of data collection forms (called "panels"). Any given panel may not have sufficient capacity to hold all the data for a given visit, but there can be a number of different panel types associated with each visit (e.g., blood sample and urine sample analyses). Thus as a trial progresses, each patient develops a collection of each panel type, with the occurrences of each panel type arranged in time sequence. In preparation for data analysis, the information in the panels may be retrieved from the data base and arranged in a worksheet (data matrix) that is convenient for the analysis procedures.

As previously mentioned, data retrieval and analysis for large clinical trials can consume a large amount of computer time and resource. However, subjects for most trials divide naturally into groups, e.g., control and experimental groups. The CLINFO system allows for this grouping, or subsetting, of subjects. When appropriate, data for each group can be retrieved independently, thus lessening the load on the computer system for each retrieval.

The interviewed investigators were asked specifically about their use of each of the statistical tools available in CLINFO, and about whether there were any other statistical methods they used that were not mentioned. In all but two cases, the majority indicated that they used all the kinds of statistics available in the system, although only a few had a CLINFO system available to them. The first exception was cross-tabulations, and the nonuse of that technique is inconsistent with the fact that they did use the chi-squared test, which operates on the kinds
of arrays produced by cross-tabulations. The second exception was life table analysis, which was used by only 28 percent of the respondents. Analysis of covariance was used by the majority of investigators, but it is not now available as part of the CLINFO system. In response to a question about whether there were other tools that the investigators used but were not mentioned, there was no consistent pattern for those who replied positively, and only 31 percent could identify other statistics that they use. It would therefore seem that with the addition of analysis of covariance, the CLINFO statistical tools are sufficient. It should be kept in mind that the respondents were medical investigators and that the same questions put to statisticians might result in very different responses.

The CLINFO system provides many functional capabilities useful for managing clinical trials data. Indeed, data for a number of trials have been managed using the CLINFO systems now installed. Additional functional capabilities would enhance the usefulness of the system in supporting clinical trials.
Chapter 5

RECOMMENDATIONS

Clinical trials are an important bridge between basic medical research and health care practice. They are highly visible and receive a significant portion of the medical research funding in this country. The GCRCs provide an environment matched by few other institutions for the conduct of high quality clinical trials.

The recommendations in the later sections of this chapter are directed toward making the conduct of high quality clinical trials in the GCRC environment more productive and efficient. The investigators who are interested in and capable of conducting these trials face many disincentives. Clinical research tends to take more time, cost more money, involve more uncontrollable factors, require more approvals, and yield fewer publishable results than laboratory or animal research. Investigators interested in conducting clinical trials face the additional disincentives that such trials entail a large administrative and information processing component and generally receive low marks from GCRC site review teams. While no set of resource improvements can completely overcome these disincentives, some improvements should facilitate the conduct of important trials by interested investigators.

The first section of this chapter describes the context for GCRC support for clinical trials, including the kinds of support that are appropriate and the benefits and limitations of that support. The second section discusses some information processing aids for clinical trials that deserve further exploration. The third section describes four models for GCRC Program support for clinical trials, with each model an incremental extension of the ones preceding it. The remaining sections contain specific recommendations.

The recommendations in this chapter are of two kinds: those that could result in changes that directly benefit an investigator carrying out a clinical trial, and those that could lead to improvements in the effectiveness and efficiency with which GCRC resources are used. The latter kind of recommendation has the potential for benefiting the clinical trials investigator indirectly, namely, by making additional personnel time or facility-use time available to his trial. For example, a reduction in the time a dietitian must spend doing manual calculations would leave her more time to counsel trial subjects about compliance with a therapeutic diet.

CONTEXT FOR GCRC SUPPORT FOR CLINICAL TRIALS

The precise treatment and observation requirements of a clinical trial may exceed the capabilities of a regular hospital ward and its staff. House and support staff members change frequently and their replacements may not be familiar with the protocol, and patient-care demands may cause staff to overlook research requirements. Further, funding for a clinical trial typically does not cover inpatient hospitalization charges, and these must be paid by another source, such as a third-party payer or the patient himself.

The GCRCs can provide the kind of inpatient facility needed for many trials. The staff members usually work only in the GCRC, have a much lower turnover rate than for hospitals as a whole, and are specially trained for research. The GCRC grants provide funds to cover
recommendations

inpatient hospitalization and testing for research purposes, and thus can fill in a missing part of the funding for carefully selected clinical trials.

GCRC support for clinical trials is valuable for a number of reasons. A GCRC provides resources that would otherwise not be available. It provides continuity and a dedicated research environment through a highly trained support staff that individual investigators could not develop and maintain even with adequate funding for individual clinical trials. It enables investigators to carry out small trials and to pilot-test trial ideas quickly, before major funding is sought to pursue these ideas. A GCRC is particularly valuable for younger investigators who may use its facilities to gain experience and build research credibility before applying to an institute for funding.

A GCRC cannot substitute for individual research funding. It is best suited to providing resources that are useful for many investigators and for many research studies, but cannot be justified by the requirements of an individual investigator. To the extent that other funding sources benefit from the sharable resources provided in GCRCs, these other sources should be encouraged to support the development of GCRC resources.

GCRCs should continue to support trials that are of the magnitude of the trials and other clinical research studies now using these centers. Larger trials involving thousands of subjects might well swamp GCRC facilities. These large trials might use GCRC facilities on a limited basis for dealing with special problems (e.g., an unanticipated reaction to medication), but they cannot use GCRCs for the bulk of the trial interventions and observations.

GCRC Program funding is limited, the number of GCRCs has been decreasing, and the amount of support for the remaining GCRCs does not cover as much as it once did. Because this trend is likely to continue for at least the next few years, we have constrained our recommendations to fit within the general level of funding currently available. Some of the recommendations require little or no additional funding, and can be implemented by reallocating existing resources, as, for example, changing personnel responsibilities at individual GCRCs. Other recommendations, such as the addition of the equivalent of a full-time support staff member at selected GCRCs, require only a marginal increase in expenditures. Still other recommendations involve a modest initial expenditure that might well be recovered over time through more efficient use of GCRC resources (e.g., the addition of management aids to facilitate expense tracking and cost recovery as appropriate). Where possible our recommendations build upon existing or planned resources instead of suggesting more expensive new initiatives.

information processing topics for further exploration

Before we address models for GCRC Program support for clinical trials and present specific recommendations, we will describe some ideas for information processing aids that deserve further exploration, but about which we need more information before we can evaluate their usefulness. These aids include the equivalent of a computerized resource utilization calendar with associated appointment lists, work and resource load predictions, and other forms of reminder information. In combination with the calendar, a collection of files containing mailing and telephone number lists would facilitate the generation of form letters and appointment reminders. The computerization of data form design and printing and of report generation would also relieve some of the difficulties mentioned in our interviews. Finally, the existence of CLINFO systems makes it possible to explore the utility of data structures and their relation to analysis techniques in advance of committing to their use for data collection and storage.
The CLINFO system managers and developers of future refinements to the CLINFO system could implement some of these aids as Basic programs and evaluate their utility locally. If of use locally, these programs could then be shared with other CLINFO sites to determine their general utility and appropriateness for distribution to all CLINFO sites. There is a precedent for this kind of activity. Certain aids (e.g., a few system manager utilities and a GCRC census program) were developed by individual system managers for the CLINFO prototype system and distributed to and used at the other CLINFO sites.

**Computerized Appointment Calendar**

Each GCRC has a method for scheduling beds that may involve the use of the equivalent of an appointment book, or a wall chart on which the rooms and beds are pictorially represented and on which a short time sequence is given of the predicted use of each bed. Usually an appointment clerk consults the chart (or book) to determine whether a bed will be available when needed, and must take into account such constraints as not placing children and adults in the same room even though a bed is available. An appropriate bed is then reserved for the required amount of time. A computerized calendar could provide a chart, such as the one in Fig. 5.1, depicting the use of GCRC beds in the time period desired.

The appointment clerk might visually scan such a chart or ask the computer to find an appropriate slot and report success (and print an appointment slip and record the appointment in the chart) or failure (which would mean that the clerk would have to change the time frame or adjust other appointments). At the clerk's request, the display could be changed to provide names and telephone numbers so that the subjects could be contacted to arrange for possible rescheduling. Figure 5.2 illustrates one possible display of the data.

Information about each subject's protocol could also be stored in the calendar. The computer system could then produce a weekly report for the head nurse, the dietician, the laboratory technicians, and the GCRC administrative coordinator, showing projected bed occupancy,

```
   M  T  W  T  F  S  S  M  T  W  T  F  S  S  M  T  W  T  F  S  S

ROOM 101

ROOM 102
BED B  M  M  M  M  M  M  M  W  W  W  W  W  W  W  W  M  M

ROOM 103
BED B  B  B  B  B  W  W  W  W  W  M  M

Note: B=boy, G=girl, M=man, W=woman
```

Fig. 5.1—Bed-usage chart
special meals, special nursing and medical procedures, and the kinds of laboratory tests that will be required in the next week.

Such a computerized calendar could also produce a form letter to be sent to each subject to remind him of his appointment and any special actions he should take before arriving (e.g., complete a diet history for the week prior to his appointment).

Report Generation

The current modes of printing results on the CLINFO system were designed for individual researchers whose needs were primarily for recording data and analytic results. Reporting to supervisory or funding organizations is done by abstracting and typing data in a more formal fashion. Part of the work done in the production of the formal reports could be done by a generalized report generator. The concept of a report generator is certainly not new, but its application to systems like CLINFO would enhance their value to clinical trials.

The simplest example of such a generator would take the contents of a CLINFO worksheet and produce a report formatted according to a set of instructions that are retained by the computer. Then each time that report is required, the latest data can be collected in the worksheet and the instructions reinvoked (much like a CLINFO "response file").

More complex generators could process the entire database each time a request was made to produce summary statistics, patient accrual information, and data required for patient safety monitoring.
Data Form Generation

Data for a trial are not simply entered via a computer terminal, but are usually captured first on a printed data collection form. Several users of the CLINFO system have found it convenient to label the rows and columns of a worksheet (similar to a data flowsheet), to print that worksheet, reproduce the printed form, and use the reproductions as data collection forms. Those data can then be entered directly from the forms into a corresponding CLINFO worksheet via a computer terminal. The data forms and the worksheet correspond exactly in format so that the data clerk has little trouble in entering and checking the data. The generalized report generator for worksheets mentioned above could be extended to produce a properly formatted data collection form from such an empty worksheet so that the appearance of the form is more familiar to data collection personnel.

A more complex form layout procedure would allow an investigator to design a data collection form on a CRT display terminal by simply positioning the typing cursor and typing the appropriate text. The values to be entered in the data fields could be referenced directly to the database schema, and the appropriate range and encoding values could be produced automatically. When the investigator was satisfied with the result, he could then have it printed for later reproduction. The computerized form, along with all the supporting data (e.g., references to the schema), could be stored for later recall and modification.

An attractive feature of the blank worksheet data form is its exact correspondence to the computer data entry procedure. The more complex system described in the preceding paragraph could also be extended to generate automatically a data entry computer program that presents the form on the CRT terminal and prompts the data clerk for the values required for each entry. The full editing facilities of the schema could still operate while the correspondence between the paper form and the CRT form provides a large amount of context for the clerk.

Exploration of Data Organization Alternatives

Experience with the CLINFO schema (data base description) has shown it to be a valuable tool for planning and organizing the data to be collected during a study. However, decisions about that organization made at the beginning of a study may result in awkward data manipulation requirements when the time comes to do the analysis. For example, suppose a subject may report multiple symptoms, such as fever, tenderness in the abdomen, and nausea. One data organization could be to define several distinct symptom items, e.g., SYMPTOM1, SYMPTOM2, and SYMPTOM3, and assign values according to the symptoms the subject reports. In this organization, SYMPTOM1 might be assigned the value "fever" and SYMPTOM2 the value "abdominal tenderness" for subject 1, whereas SYMPTOM1 might be assigned the value "nausea" for subject 2. Another organization could be to define items corresponding to fever, abdominal tenderness, and nausea, and to assign the value "yes" or "no" to each for each subject. The first organization could make it awkward to answer questions about which subjects had a fever. If the investigator were not careful, he might be required to look at the values of all the symptom items for all the subjects. The second organization would require the investigator to look only at the fever item for each subject to answer the question. The CLINFO data organization and retrieval facilities are highly flexible but cannot cover the myriad of possibilities in medicine. In other systems, the usual solution to this problem is to have a computer programmer produce a procedure for solving the problem. Systems like CLINFO are designed to avoid interposing a programmer between a researcher and his data, and the price for that benefit is some degree of inflexibility.
One solution is to encourage the investigator to describe his data via the schema, enter some sample data, and attempt to retrieve and analyze them. Another approach might be to extend the concepts already used in the schema (e.g., asking for a value range for an item) to include capabilities such as asking whether the investigator expects to create sets of subjects depending on the value of an item, or what statistical tests he plans to apply to an item. The result would be some advice or cautions about the organization based on the system’s knowledge of the requirements of the analytical procedures and on the possible implications of a specific data organization. Of the suggestions presented in this section, this latter idea would require the heaviest investment in research and development.

MODELS FOR GCRC SUPPORT OF CLINICAL TRIALS

As currently implemented, the GCRC Program provides beds and a highly trained nursing staff that can be used to support clinical trials. Many centers provide a diet kitchen and a dietary support staff, and some centers provide a limited amount of laboratory work as well. Some centers have outpatient areas, but these tend to be limited and to have no special staff support. A few centers have a CLINFO computerized data management and analysis system, and a few have caseworkers who may perform as coordinators for clinical trials and other studies.

An improved model would augment the current resources with a research data coordinator. As described in more detail in a later section, a data coordinator would be responsible for keeping track of data forms and seeing that they were filled in at the appropriate times. This person would support many trials, and any trial requiring a large share of a coordinator’s time would be expected to fund its own coordinator.

A second improvement would include some computing capabilities. By the mid-1980s, CLINFO systems are expected to provide computing capabilities for about one-third of the GCRCs. Where currently installed, CLINFO systems now provide data management and analysis facilities that are useful for many clinical research studies.

A third extension would provide statisticians, programmer/analysts, and other personnel with expertise in experimental design. They would be available on a limited but regular consulting basis.

A fourth model would further augment GCRC resources with extended CLINFO and other data processing capabilities. These extended data processing capabilities include improved data editing, document tracking, randomization, sample size determination, diet analysis, and resource management.

RECOMMENDATIONS ABOUT PERSONNEL

Clinical Trials Coordinator

A typical investigator strongly agrees that clinical trials require a large amount of administrative and managerial effort. Much of this effort involves information processing. Because of time and staff limitations, he may be unable to conduct important clinical trials.

A typical investigator thinks that having a person available to act as a data coordinator
for clinical trials using the GCRC would be very useful. Such a person could coordinate a number of different trials, could provide continuity and consistency, and could substantially reduce the information processing burden faced by the investigator.

A data coordinator should be familiar with the active clinical trials protocols and their data collection requirements. She should be responsible for maintaining data collection forms, making sure that they are filled in accurately, completely, and consistently. The coordinator may fill in forms herself, e.g., by abstracting from subjects' medical records or by interviewing outpatients, or she may review forms filled in by other staff, such as subjects' charts filled in by nurses. She should be aware of laboratory work requests and make sure that the resulting data are received and properly recorded.

A data coordinator is not a general purpose research aide, and should not devote a substantial amount of time to any one investigator or any one clinical trial. Investigators whose clinical trials activities require considerable administrative support should provide their own staff. Such investigators usually have research nurses or other support staff, and should continue to use their own staff members in the GCRCs. Investigators who need an aide to draw blood, give medication, recruit subjects, or type papers should find other sources of support and should not expect a GCRC data coordinator to do those jobs.

To be effective, a data coordinator would need to work closely with each investigator before he activates his clinical trials protocol. It is the investigator's responsibility to provide the details necessary for the coordinator to do her job. This interaction could lead to the development of a protocol notebook and, at those sites having a CLINFO system, a CLINFO data base schema for the trial.

Protocol notebooks are already in use at GCRCs, and a general outline of the contents of these notebooks would be a useful guide to the investigator who must supply the information. The coordinator might maintain these notebooks and store copies of all completed data forms with them.

Establishing a CLINFO schema before the trial starts not only encourages the investigator to think through exactly what information he wants to collect, but can also facilitate data forms design and data collection. The CLINFO system manager would interact with the coordinator and assist in the initial schema design, forms design, and other data-related efforts. As data are collected, the coordinator could use CLINFO capabilities for data editing and document tracking.

The particular GCRC staff position that a data coordinator holds will vary from center to center. In those GCRCs with outpatient facilities, the coordinator might be part of the outpatient staff, for example a secretary/receptionist, an outpatient nurse, or a caseworker or social worker. If the GCRC has facilities and staff only for inpatients, the coordinator might be a member of the nursing staff or a technician. For some centers, a coordinator might be a completely new position. In any case, the data coordinator position does not necessarily require a licensed nurse, social worker, or technician. It does require someone who has skills in organization and coping with details and some familiarity with medical research.

In some centers, several persons may serve as data coordinators. Each would have primary data coordination responsibility for a group of protocols. This arrangement has some similarity to the primary care nursing model. Indeed, if there were sufficient staff, nurses or others already present in the GCRCs could serve as data coordinators.

We recommend that the GCRC Program provide research data coordinators in the GCRCs to support clinical trials.
Consultants

A typical interviewed investigator thinks that having a part-time biostatistician regularly available during the course of a trial would be very useful. He thinks that a biostatistician and computer scientist would also be very useful for a short but intensive period during the planning stages. Some GCRC investigators already make use of biomedical scientists with experience in experimental design, statistics, and information processing. Although these people are typically not supported out of GCRC funds, they are often readily available to GCRC investigators who want to consult or collaborate with them. At those institutions without such relationships between biomedical scientists and GCRC investigators, the GCRCs should make special arrangements to establish them. One way to do this would be to fund statisticians, programmer/analysts, and other biomedical scientists to be regularly available in the GCRC on a consulting basis. This availability would be similar to faculty office hours, i.e., at a fixed time on a regular but limited basis. Office hours would be funded by the GCRC. Providing funds to support additional contact on a consulting basis or to support collaborative efforts would be the investigator's responsibility. This approach has the major additional benefit of encouraging investigators to seek statistical and other guidance before they begin a trial.

We recommend that the GCRC Program fund biomedical scientists to be available in the GCRCs on a regular, but limited consulting basis.

RECOMMENDATIONS ABOUT COMPUTER SYSTEM SUPPORT

New functional capabilities can be made available for clinical trials data processing in a number of ways. They may be added as integral parts of existing CLINFO functions, e.g., by incorporating new statistical analysis functions. They may be added as new CLINFO functional areas, e.g., as a new activity to support consistency checking among several data items or for a single item over time. New capabilities may also be implemented outside the CLINFO system but on the same computer, or on another computer system.

Analysis of Covariance

Analysis of covariance is used by 58 percent of the interviewed investigators, but it is not now included in the CLINFO statistical routines. The coordinating center statisticians we interviewed during the first year of the project also identified analysis of covariance as a tool frequently used with clinical trials data.

Covariance, which combines the capabilities of analysis of variance and linear regression, has many uses in clinical trials applications. It can be used to increase the precision of treatment comparisons and reduce the experimental error in randomized trials. It can be used to adjust treatment comparisons for possible bias resulting from an imbalance of key outcome factors across treatment groups. It can be used to help explain treatment effects in randomized trials and to examine and compare regressions involving subsets of the trial data. A description of the uses of analysis of covariance is given in Ref. 11 and the details needed for a computer implementation are discussed in Ref. 12.

We recommend that analysis of covariance be added to the CLINFO analysis activity.
Data Editing

The CLINFO system provides limited screening capabilities during data entry. Individual data items may be checked to see if they are in a prespecified range, if they correspond to one of a list of prespecified codes, or if they are in the appropriate format to be dates or times.

Clinical trials data typically receive more extensive data editing than is now directly provided in the CLINFO system [2]. In addition to CLINFO-type screening of individual data values, data processing personnel typically cross-check for consistency in the values of a single variable collected repeatedly over time, and for fixed relationships among a set of variables. Cross-checking is also important in determining or verifying subject eligibility. For example, values for a subject’s weight obtained weekly for 3 months might be checked to determine if any value is more than 10 pounds from the mean. A check might also be made to verify that the drug and dosage given at each visit are consistent with the protocol requirements for the treatment arm to which the subject has been assigned.

Data cross-checking can be done through a series of existing CLINFO activities, but it would be a cumbersome process if extensive checking were often necessary. If the data were in a CLINFO data base, the appropriate values could be retrieved, placed in a worksheet (data matrix), and manipulated and compared through various arithmetic and logical operations to produce a derived variable indicating whether the screening criteria were met. An alternative procedure would be to use the subsetting capabilities to produce a set of subjects whose data did or did not satisfy certain criteria, and then to retrieve and review the appropriate data only for that set of subjects. Although the steps to carry out these procedures could be made into a CLINFO response file to eliminate much of the user typing, cross-checking would still be time-consuming.

The addition of a new CLINFO activity module could provide for easier and more extensive cross-checking. Such a module would permit specification of arithmetic and logical expressions to be compared with the data base in a one-pass survey mode, rather than in a series of operations as must be done now. This new activity might be designed so that once the user completes the specifications, he can request that the data base survey phase be run at a later time, much like the current merge of newly entered data with an existing data base. Another useful function might be provided as a utility program that would scan the entire data base and check every item value against all the relevant screens (both individual item and multiple item screens).

Data cross-checking is often done manually or with the aid of a few special purpose computer programs. Although there is great interest in the problem, there are no good models for easy-to-use, general purpose data cross-checking programs. Some approaches to the problem are discussed in Ref. 13. The Society for Clinical Trials is a good vehicle for encouraging further discussion and generating ideas for future development.

We recommend that the GCRC Program encourage discussion of requirements for general purpose, data cross-checking procedures at meetings of the Society for Clinical Trials. We further recommend that, for the purpose of checking data consistency, an additional activity be added to the CLINFO system to permit specification of logical expressions to be compared with a CLINFO data base in a survey mode.

Document Tracking

The major information processing objective of a clinical trial is the organized collection of reliable data that can be analyzed to produce valid information. In addition to careful recording and editing of the data, it is important to know that data collection is timely, that the forms
and documents containing those data are correctly managed, and that the data base is an accurate record of the data collected.

Keeping track of data collection forms and their status is an important part of data quality control for a clinical trial. Although this activity has its greatest visibility in data coordinating centers associated with multicenter clinical trials, it is important for single-center clinical trials as well. Indeed, 93 percent of the investigators interviewed thought that a document tracking system would be useful or very useful to support their clinical trials.

A document tracking system for clinical trials serves two purposes: to determine the status of data collection forms and to provide an audit trail of changes made to the clinical trial data base as a result of changes in the status of forms. The tracking system should provide the user with a number of useful capabilities:

- To anticipate when a form should be completed.
- To detect if a form is overdue or has been completed.
- To determine if the data on the form have been entered into a computer system.
- To determine if the entered data have passed data screening or if they have errors or omissions, and if corrections have been requested, received, and entered.
- To verify that the form is completely processed.
- To locate the physical document.
- To check the status of the data base (e.g., to determine which corrections have been made and which have not).
- To trace all data base modifications so that incorrect changes to the data base can be detected and corrected.
- To determine when and by whom changes to the data base were made, as well as what the new and changed data values were.

Although providing an audit trail would require some additional implementation, tracking the status of data forms can be done by using the current capabilities of the CLINFO system. Tracking information can be integrated into the trial data base by defining a status panel as part of the CLINFO schema for the data base. Each occurrence of a data form would have a corresponding instance of a status panel. The panel items would include the following entries:

- Form type.
- Date form is/was due.
- Date form was completed.
- Form status (e.g., not yet due, due, overdue, received, entered, screened and errors found, screened and no errors found, corrections requested, corrections received, corrections entered, corrections screened and errors found, corrections screened and no errors found, completely processed).

Each status panel instance would have the corresponding form due date as the date associated with the panel. To be of greatest value to the tracking system user, all status panels should be entered, with an appropriate due date and status of "not yet due," at the time that a subject is first entered into the trial. However, changes in schedule might necessitate deleting and reentering status panels in order to change the panel dates. An alternative to this would be to enhance the CLINFO retrieval, subsetting, and other relevant activities to permit restricted retrievals on date items. This would eliminate the need to change the panel date, and the key date (the date the form is due) could then be contained in the panel as an item.

An audit trail could be implemented as an audit file associated with the CLINFO merge program. While doing the standard data base update, the merge program could also write a
file recording all changes (including additions) to the data base during the update process. Each change should be identified by subject, panel and item name, old and new value, date and time of entry for old and new value, and identity of enterer of old and new value. Because this file could become very large, it might be stored offline, e.g., on magnetic tape and/or printed and maintained in a notebook, rather than all of it being kept available as an online computer file.

We recommend that an audit trail capability be added to the CLINFO merge program. We further recommend that the possibility of modifying the appropriate CLINFO activities to permit restricted retrievals on dates as items be explored.

Sample Size Determination

Before undertaking a clinical trial, an investigator must determine if enough subjects will be available in a reasonable time. Sample size determination is the process of determining how many subjects are enough. Before an investigator can determine sample size, he must specify the amount of expected treatment differences, the power and significance level desired, and the amount of expected variability in observations. Given these specifications, he can then determine by himself or with the aid of a statistician the appropriate sample size for his trial.

Because the specifications are only estimates, it is important to determine how sensitive the sample size is to small changes in the specifications. The final choice of sample size can then be made with knowledge of that sensitivity. One factor in the final decision to undertake the trial is how the desired sample size relates to the number of subjects and amount of resources available.

A sample size calculation program would be easy to implement and would probably receive widespread use. It would not only eliminate the need for the manual, error-prone calculations done now, but could also be used to explore the sensitivity of a particular sample size to the values of the parameters used in the calculation. Such a program could improve an investigator’s awareness and understanding of the kinds of questions a statistician might ask during a planning discussion.

A program to perform sample size calculations, given the necessary specifications, could be implemented readily on the CLINFO computer. As output it should provide a table showing sample sizes for the parameter values specified and for nearby values as well. Initially, this program could be restricted to the use of the CLINFO system manager. He would find it a valuable tool for helping CLINFO users plan a new clinical trial. Later, this program could be made a part of the CLINFO describe activity. To use the sample size calculation subactivity, an investigator undertaking a new clinical trial would have to contact the system manager and have him allocate a directory for the investigator’s trial. This might encourage investigators to think about using the CLINFO system before the trial begins rather than waiting until all the data are collected.

Two alternative program approaches should be considered. One approach is to write a program that simply asks for specific inputs and produces a table of sample sizes as output. The other approach is more tutorial and provides more explanation about the required inputs and program options. An explanation of sample size calculation suitable for clinical investigators is given in Ref. 14.

We recommend that a sample size calculation program be made available on the CLINFO computer. After the program has been thoroughly tested and evaluated, and has been shown to be useful, consideration should be given to incorporating it into the CLINFO describe activity.
Randomization

Randomization is a procedure for allocating treatments to experimental subjects so that all allocations have a predetermined likelihood of occurring within the constraints of the trial design. Randomization eliminates bias in the allocation of treatments and provides a logically valid basis for the use of statistical inference to compare treatments.

Randomization can be done in many ways, e.g., by using a random number table or a computerized random number generator. A common problem with the use of tables or generators is that they may produce long runs of assigning the same treatment to each successive subject. To avoid this problem a restriction is placed on the randomization so that after every \( n \) assignments the treatment groups will be balanced, i.e., there will be an equal number of subjects in each treatment group. (Typically, \( n \) is twice the number of treatment groups.) A thorough discussion of the relevant considerations is given in Ref. 15.

About half of the trials described by the investigators we interviewed were randomized. A program that provided stratified, balanced randomization would be easy to implement and its availability could simplify the mechanics of randomization for many investigators.

A program to provide stratified, balanced randomization could be implemented readily on the CLINFO computer. It would take the number of treatment groups as input, and provide balanced blocks of treatment assignments as output. Initially, the program could be provided as a separate Basic program, and its use could be restricted. Like the sample size determination program, this would be another tool for the CLINFO system manager. Later, after it is evaluated, the randomization program could be provided as a CLINFO activity. To avoid bias in subject selection, the investigator should not know beforehand to which treatment group a subject being screened for eligibility will be assigned. Thus the output of the randomization program must receive special handling. For example, each assignment could be sealed in a numbered envelope, to be opened only after determination of subject eligibility.

A variation of this program would provide for balanced randomization, but would make only one treatment assignment available at a time. To make this approach work, each execution of the program would have to be associated with a particular clinical trial. Thus if this variation of the program is implemented, it should be as a CLINFO activity. The first time the activity was used, it would request the number of treatment groups and generate, but not display, the first block of assignments. At each subsequent use, it would request a subject identification, check to see if that subject had been entered into the data base and whether or not a treatment had been assigned, and then display the next treatment. If necessary it would generate the next block of assignments. Provision could be made to allow multiple treatment assignments if necessary for cross-over studies or studies with a progression of treatments.

We recommend that a randomization program be made available on the CLINFO computer. After the program has been thoroughly tested and evaluated, and has been shown to be useful, consideration should be given to creating a CLINFO activity following one of the two models described.

Dietitian Assistance

Dietitians spend considerable time searching standard nutritional composition tables, transcribing values, and calculating the amount of various nutrients in a particular diet. Because of the time involved in analyzing diets, a dietitian may be limited in the range of possibilities she can consider and may not be able to provide timely feedback to research subjects. For example, an outpatient may keep a diet history (i.e., a record of what and how much he has eaten) between visits and present it to the dietitian so that she may determine
if the subject is complying with a prescribed diet regimen. Unfortunately, the volume of information the subject provides is often too great for the dietitian to analyze manually during the visit, and thus subject feedback must be delayed until the next visit.

Computer programs to aid the GCRC dietitian in food composition analysis are readily available. These programs vary in size and capability, and are available for desk-top computers, minicomputers, and mainframe computers. A typical GCRC dietitian may have tested one of these programs in a lipid clinic or some other unit of the hospital complex. What deters her from using a program already available in her institution is that no funds have been budgeted for buying computer time for dietitian use. This problem can be eliminated by making a food composition analysis program available on the CLINFO computer or another computer in the GCRC. The use of such a program could substantially improve the productivity of GCRC research dietitians.

One program that runs on a Digital Equipment Corporation PDP-11 computer, the host computer for the production CLINFO system, is the HVH-CWRU Nutrient Data Base, developed and maintained by the Division of Nutrition, Highland View Hospital, and the Department of Biometry, School of Medicine, Case Western Reserve University, Cleveland, Ohio. For those GCRCs that will not receive CLINFO systems, funds should be provided to make a food analysis computer program available to the dietitian. This requires obtaining (and, if necessary, adapting) a program to run on a computer in the GCRC or elsewhere in the institution, if such a program is not already in use, and providing funds to use that computer.

We recommend that the GCRC Program identify and evaluate the available food composition analysis programs and make appropriate programs available to all GCRC dietitians.

GCRC Management Aids

A typical administrative coordinator identifies fiscal management as the most time-consuming of her activities. Careful accounting is necessary to prepare and revise budgets, track research expenditures, and recover costs for nonresearch-related activities. For example, a coordinator must distinguish among three categories of GCRC patients, research ("A"), research service ("B"), and nonresearch ("C") patients. Depending on the patient category, the charge for a particular service may be billed either to the GCRC grant or to the patient or a third party insurance carrier.

The coordinator's efforts to manage GCRC finances are often hampered when she must interface with a poor hospital information system. The hospital system provides billing information (e.g., charges to the GCRC grant for beds and ancillary services) and income information (reimbursements to the grant from third party carriers). The major problems that confront the coordinator are that the information may not be provided in a timely fashion and may not be accurate. For example, information may be received 3 or 4 months after a patient is discharged, the services billed for may not be the same as the services performed, or the GCRC grant may be charged for hospital care costs that should have been billed to the patient's third party carrier. Although a coordinator can keep manual records that accurately account for grant funds, the problems with the hospital information system may prevent her from having the up-to-date information necessary for effective planning.

In addition to planning and tracking GCRC expenses and income during the year, the typical coordinator devotes a month or more each spring to producing her GCRC's annual
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The coordinator or another staff member must review and tabulate information from a year of GCRC use. This includes bed use, laboratory tests performed, protocol activity, publications, and financial data. Because annual report requirements change from year to year, the coordinator cannot always anticipate what will be needed. Thus, even if she regularly categorizes and tabulates information during the year, she may still have to review many paper records to obtain newly requested information. Another source of delay comes from some investigators who do not provide protocol progress summaries, funding information, and publications when requested. Finally, the mass of information collected must be arranged, edited and probably retyped and proofread several times before the final version emerges.

An aid that would facilitate fiscal management and annual report generation (as well as the even more demanding 5-year grant renewal application) could contribute to improved GCRC productivity. It would free some of the time the administrative coordinator and other staff spend on these tasks, and enable them to address other problems. It would also provide up-to-date information for management decisions regarding resource allocation. This would enable the director, his advisory committee, and his staff to take actions to maximize the use of GCRC facilities and to avoid the extremes of overspending or underspending grant funds.

A GCRC management aid could be provided via an inexpensive microcomputer or minicomputer system and the appropriate applications software. For those GCRCs with CLINFO systems, additional software could be developed to provide a management aid on the CLINFO computer.

Some of the applications software is already available for a variety of microcomputers and minicomputers. Word processing software is widely available. Indeed, the CLINFO system has an associated text editor. For those GCRCs having a CLINFO system, it could be used to verify that the facilities of a text editor are of value and should be made widely available.

Other software, developed for small businesses, may also be of use to a GCRC. This includes the inventory control, accounting, and budgeting packages that are available on many different small computers. Still other software, e.g., resource management software for tracking GCRC utilization, might have to be developed. However, some development work in this area has already been done at the University of Washington CLINFO site.

A few investigators (including program directors) have begun to inquire about and purchase microcomputers. Among the applications of interest to them are some, like word processing, that are also of use in GCRC management. Because of their relatively low cost, it is likely that these microcomputers will proliferate in the medical research environment and that the NIH will receive numerous requests to support software development for them. It is not too early to encourage selection of compatible computers and software packages.

We recommend that the GCRC Program investigate the feasibility of providing support for a computer-based management aid for a large number of GCRCs.

RECOMMENDATIONS ABOUT DEVELOPING INVESTIGATOR EXPERTISE

As cited earlier, one of the GCRC Program objectives is "to encourage, develop, and maintain a national corps of expert clinical investigators [3]." To develop clinical investigators with expertise in the conduct of clinical trials involves special attention to education about research methodology.

One way to provide education in research methodology is through a formal institutional program. The GCRC Program could fund the development of instructional materials and the
conduct of workshops and seminars for investigators and GCRC staff. One useful instructional aid is a handbook on clinical trials methodology, which would draw together in a single document much of what an investigator should consider in planning and conducting a clinical trial. It would both provide information to the investigator and prepare him to consult with statisticians, programmers, and others as needed.

A more ambitious solution, and one which would require support from sources outside the GCRC Program, is to develop a curriculum and certification program in research methodology. Typically, research methodology is not part of the medical school curriculum. The level of investigator expertise in research methodology varies greatly, depending on the quality of on-the-job research training he received after medical school and his own diligence in seeking out information. The lack of expertise is particularly pronounced for clinical trials, in which nonmedical considerations play a more important role in the successful execution of experiments than in other clinical research. A program in research methodology would provide training in experimental design, statistics, information processing and other nonmedical disciplines necessary for the conduct of clinical trials. Such a program would benefit all clinical investigators, and would be particularly useful for those involved in clinical trials.

Another approach to developing a corps of investigators with expertise in research methodology is to make additional people experienced in the appropriate disciplines readily available in the GCRCs. The typical interviewed investigator has had a limited amount of training in statistics and the use of computers. He would like additional training in these areas, provided it is in the context of his research. If biomedical scientists are supported in the GCRC on a limited consulting basis (as was recommended in an earlier section), they could also contribute to investigator training.

A computer system with the appropriate capabilities can supplement the other educational methods. An investigator can gain insight into problems of data collection, management, and analysis by working with his own data, as is possible with the CLINFO system. Tutorial exercises can be established around a demonstration or instructional data base. Personnel associated with the computer system, e.g., the system manager for a CLINFO system, can often provide additional guidance in information processing and statistics.

An experienced research data coordinator is also an educational resource. Her experience gained through coordinating many trials will enable her, for example, to point out before a trial begins what sort of information may be difficult to collect and how a form might be improved.

The combination of instructional guides, resource people, and computer systems creates an educational environment that facilitates investigator learning of research methodology and practice of what he learns. Such an environment would also make it possible for an investigator and one or two of his staff members to act as both a clinical center and a coordinating center for a small multicenter trial, and thus would encourage collaborative studies.

We recommend that the GCRC program explore ways to develop materials and programs to improve investigator expertise in the nonmedical aspects of research methodology.
REFERENCES
