Pediatric Gastroenterology Collaborative Research Group (PGCRG) Success and Failures in Multicenter Clinical Trials

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Multicenter clinical trials offer great opportunities to answer clinical research questions through greater access to patients and pooling of data from multiple institutions. Unfortunately, these benefits are accompanied by many challenges in dealing with different sites and different investigators (1). Even the most experienced investigator and sponsor may find surprises and problems in selecting collaborators and in the recruitment of patients. In pediatrics, collaborative research is often a necessity because so many problems we encounter are relatively uncommon. Although placebo-controlled trials can reduce the number of patients needed, they are not always an option for studies involving children. The American Academy of Pediatrics has outlined appropriate instances for placebo trials (2), but pediatricians often are reluctant to enter children in such studies because of potential or perceived harm from offering no treatment.

In addition to greater patient access, multicenter trials offer a number of other advantages (Table 1) (3). Broad patient representation may be a requirement for some protocols, and collaboration regionally, nationally, or internationally can answer this need. Selecting study sites in different clinical settings is another way to add validity and generalization to the results. The choice of a private practice setting rather than an academic setting might be more representative of real-life situations and give a study added significance.

Although the need for a multicenter trial may seem obvious, the sponsoring agency and the principal investigator must clearly define the benefits to attract qualified and productive participants. Because multicenter studies are time-consuming and often generate extra paperwork, it may take a considerable effort to maintain interest and active participation throughout the study. One way to create this enthusiasm and a sense of ownership in a study is to include investigators from the very beginning of a new protocol. The following sections explore some of these issues in more detail. The outline used by our Pediatric Gastroenterology Collaborative Group to develop a multicenter clinic is shown in Table 2. A sample budget is shown in Table 3.
### TABLE 1. Selected advantages and disadvantages of multicenter clinical trials

<table>
<thead>
<tr>
<th>A. Advantages</th>
<th>B. Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. More rapid patient recruitment</td>
<td>1. Administrative arrangements and management details are more complex</td>
</tr>
<tr>
<td>2. More complex protocols may be able to be conducted because of additional resources utilized for certain large trials</td>
<td>2. Costs are usually greater for the clinical trial than if the same total number of patients was studied at a single site</td>
</tr>
<tr>
<td>3. Less opportunity for one person’s biases to influence the design or conduct of the clinical trial</td>
<td>3. Statistical data analyses would be stronger from a single site</td>
</tr>
<tr>
<td>4. Greater likelihood that data processing and analysis will be conducted at a high standard</td>
<td>4. Some Ethics Committees/IRBs(^b) may insist on changes to the protocol that create major delays or are unacceptable to the sponsor or other Ethics Committees/IRBs</td>
</tr>
<tr>
<td>5. Greater likelihood that a heterogeneous patient population will be enrolled</td>
<td>5. Individual investigators in large multicenter trials receive little recognition through the publication of results</td>
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\(^a\) Reprinted from Spilker (3), with permission.

\(^b\) IRB, institutional review board.

### ACCESS TO PATIENTS

The need for a large number of patients is one major reason for collaborative research. Unfortunately, the number of subjects available for study is often hard to confirm. Clinicians often think they have patients who meet the criteria for participation, only to find that either the inclusion and exclusion criteria are too strict or that patients are unwilling to participate. In an ideal setting, an investigator would know ahead of time how many study patients might exist at each potential collaborative site. Our Pediatric Gastroenterology Collaborative Research Group has 13 centers in the United States and Canada. We have addressed this problem using computer-generated information from billing data maintained by clinic or hospital billing services. This type of data is limited and sometimes inaccurate, but it can give the number of patients with a specific diagnosis, their ages, dates of visits, and associated activities, such as procedures and laboratory tests ordered. Variables that might give a better representation of potential patients, such as severity and length of illness, current status, treatment, and so on, are not available through charge data. Another large database in many managed care settings is the pharmacy record. These computer data may include past and current medications on all patients in a given plan. For drug studies, this can help in determining patient eligibility.

Our collaborative group also has developed a software program that will allow each participating institution to gather the same data on all children with inflammatory bowel disease (IBD). Because the main research interest of the group is IBD, we think this database will allow us to estimate the number of potential patients for future studies as well as the number of centers needed and the time frame for
## TABLE 2. The Pediatric Gastroenterology Collaborative Research Group's outline for development of multicenter clinical trials

1. Protocol development
   a. The person with the greatest interest writes the first draft of the protocol and serves as Principal Investigator (PI).
   b. This first draft should:
      i. Define the problem
      ii. Review the current literature
      iii. Show why a multicenter study is needed
      iv. Outline inclusion/exclusion criteria, how the study will be carried out (methodology), compliance criteria, statistics, etc.
   c. The group meets to review the protocol and address the following issues:
      i. Is the protocol of interest and of value?
      ii. What are the clinical endpoints? What findings will be considered clinically significant?
      iii. Are diagnostic criteria acceptable?
      iv. Is the study feasible? Are there enough patients?
      v. How many centers will be needed to provide the required number of patients (the dropout rate is often 10% or more)?
      vi. Is the statistical analysis appropriate?
      vii. How much data to collect—do not overburden collaborators with too much paperwork?
      viii. Determine who will handle statistical analysis.
      ix. Who will control data, and how will data be shared?
      x. Who has publication rights?
      xi. Pick the coordinating center or organization (usually the same as PI)
      xii. Who will set up randomization and be responsible for shipping drugs?
      xiii. Decide on authorship
         1. PI should be first author
         2. List others by the number of patients enrolled
         3. Do not include if only one or two patients enrolled
      xiv. Where will the results be published?
   d. The PI revises the protocol for final acceptance.
   e. The PI submits the protocol to his or her Institutional Review Board for approval of the study and consent forms to be sure there are no significant ethical problems.

2. The PI and group then picks the appropriate centers
   a. Choice based on:
      i. Adequate patient numbers
      ii. Time, interest, and appropriate facilities
      iii. Research nurse available
   b. Each center must sign a letter of intent to carry out the study and follow the protocol
   c. All centers obtain IRB approval of the study and consent form

3. Funding
   a. The PI develops a budget for the coordinating center and collaborating centers
   b. The PI and other members of the group develop a strategy and identify potential sources for funding
      i. The PI makes initial contacts and sends the protocol for review
      ii. If pharmaceutical or governmental funding is sought, seek their advice and suggestions about the protocol early

(continued)
**SUCCESS AND FAILURES IN MULTICENTER CLINICAL TRIALS**

**TABLE 2. The Pediatric Gastroenterology Collaborative Research Group’s outline for development of multicenter clinical trials (continued)**

4. Investigator meeting when funding available  
   a. The PI or coordinating center develops case report forms, an algorithm of how the study is carried out, and a short handbook of instruction  
   b. All investigators and research nurses should be brought together to review the protocol and learn what will be needed to complete the trial  
      i. Inclusion/exclusion criteria  
      ii. Algorithm of visits, lab procedures, etc.  
      iii. Case report forms  
      iv. How drug is to be delivered and monitored  
      v. Recruiting techniques  
      vi. Reporting adverse events  

5. Enrollment of patients  
   a. Research nurse works in clinic, contacts patients, recruits, explains consent forms  
   b. Frequent contact between PI and coordinating center and participating centers  
      i. Encourage enrollment  
      ii. Answer questions  
      iii. Stimulate interest  
   c. Update all centers on progress of study every 3 months  
   d. Share any problems so all centers benefit as the study progresses  
   e. Site visits very helpful if funds available  

6. Collection and sharing of data  
   a. Coordinating center collects all data and initiates the appropriate data base and data entry, sent by mail, FAX, or e-mail  
   b. If the PI is recruiting patients, he or she must be blinded to data entry codes  
   c. Site visits or telephone calls periodically to keep interest high and to check recruitment efforts and validity of data  
   d. Any missing data are tracked immediately with the participating center  
   e. Data base is set up so that a percentage of data entry is evaluated for accuracy of entry, and parameters are established so incorrect values cannot be entered  

7. Payments to collaborating centers  
   a. Pay after a predetermined number of visits or after the patient has completed the study  
   b. Bunch payments to avoid excess work  

8. Publication  
   a. Should be prompt  
   b. Acknowledge all who participated but are not listed as authors  
   c. Acknowledge support

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completing new studies. Abstracting the information into this new data base is time-consuming and duplicates clinic chart entries. We hope that our effort will be of value in the development of future electronic medical records. If what we have learned can be transferred to these new systems, data retrieval for research purposes will become much easier and, we hope, more accurate.

**PICKING THE RIGHT CENTER**

Because institutions vary greatly in patient mix, facilities, and expertise, care must be taken in determining what type of setting is most likely to provide the right mix
**TABLE 3. Sample of clinical research budget**

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Effort (%)</th>
<th>Hours/week</th>
<th>Salary</th>
<th>Total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal investigator</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nurse coordinator</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Data manager</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretarial support</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Salaries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultant Costs</td>
<td></td>
<td>Amount</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Policy board, two meetings/year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Supplies</strong></td>
<td></td>
<td>Amount</td>
<td></td>
<td></td>
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<tr>
<td>Binders for patient data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous supplies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total supplies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Travel</strong></td>
<td></td>
<td>Amount</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigators’ meetings</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Travel for presentation of data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total travel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient costs (outpatient)</strong></td>
<td></td>
<td>Number of patients</td>
<td>Number of times</td>
<td>Cost per test</td>
</tr>
<tr>
<td>Drug dispensing/mailing</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Clinic visits</td>
<td></td>
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<td></td>
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<tr>
<td>List specific tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total patient costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other expenses</strong></td>
<td></td>
<td>Amount</td>
<td>Number of visits</td>
<td></td>
</tr>
<tr>
<td>Honorarium (per patient per visit)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telephone/fax</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total other expenses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total direct costs</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indirect costs (university overhead)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total costs</strong></td>
<td></td>
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*To reimburse the center for successful study completion.*
and an adequate number of patients. The choices between academic and private practice settings, between managed care and capitation, hospital and outpatient, regional and local, and between national and international offer a variety of types of patients and patient care settings. In multinational collaboration, and in some regional cooperative studies, issues of language, regulatory laws, clinical practice, other drug availability (including over-the-counter drugs), patient acceptance, genetics, frequency of disease, and definitions of disease are critical issues. Even with careful selection of study sites, a randomized clinical trial may lead to results that are too specific and are valid for only one or two centers. The danger in this is that the results may not be generalizable to real-life situations (4).

Any multicenter study must have a protocol that can be accepted by physicians with diverse backgrounds and practices. If a potential collaborator has trouble compromising and accepting the study design, he or she should not be encouraged to participate. Investigators must be enthusiastic about a study or they will not actively recruit patients. Over this past year, I have had the opportunity to work with the European Pediatric IBD study group in the development of a joint drug protocol for Europe and the United States. The two major issues that emerged early on were the diversity in definitions of disease and disease activity and the differences in standard medical practice. It took considerable compromise to resolve these issues, but once everyone agreed, most other issues were accepted with a good consensus.

It is not always possible to define which setting will give the best advantage for patient recruitment. A good example of this is our Pediatric Gastroenterology Collaborative Research Group experience in testing the effects of treatment on growth failure in children with Crohn’s disease. This study began with large academic teaching centers because we expected these centers to attract patients with significant growth problems. What we discovered was that many smaller institutions and private practice settings were more successful because of better patient mix and fewer commitments by the collaborator. In addition, several centers in this study were primarily referral centers and had very little long-term follow-up. Because patients came from long distances, it was impossible for them to return as required by the protocol.

Comparability among centers can be a major factor in the success and validity of multicenter studies. Different study sites need a similar level of personnel training, facilities, laboratory expertise, and treatment philosophy. Unfortunately, this type of information is rarely mentioned in publications, and a reader has to make the assumption that each center followed the protocol in the same way. Both in small studies (5,6) and in articles using meta-analysis (7), authors tend to avoid discussion of how participants were similar or different and what potential biases might have existed. This need not necessarily be the case. In a recent study of long-chain polyunsaturated fatty acids in infant formulas, multiple sites in several European countries were involved (8). There were multiple complex biochemical measures, neurologic evaluations, repeated anthropometric measurements, and varying feeding practices. The results could have been strengthened significantly by including how personnel were trained in feeding and anthropometry, describing who carried out the neurologic
and visual tests, and documenting how many laboratories were used and their levels of expertise. Although the article’s conclusions may be correct, the study could have significant flaws. It is impossible for the reader to evaluate the validity of the observations. In contrast, a study in 1993 on cow’s milk and gastrointestinal blood loss included significant details on the choice of study sites, how patients were followed monthly, and the patient mix (9). This gives the reader a real advantage in evaluating the significance of the findings.

There are other good examples of center variability and how studies might be influenced positively or negatively. In a study of low-protein formula in chronic renal disease, carried out by the Southwest Pediatric Nephrology Study Group, the authors described possible center differences in the way children were fed and how this might have influenced differences in observed growth (10). The authors also pointed out another problem in the study—refusal to follow the protocol as a result of parent and physician reluctance to carry out invasive procedures. Specifically, several investigators and parents refused use of a nasogastric tube in spite of the patient meeting the criteria for tube feeding, needing the extra nutrition, and its being part of the accepted protocol and consent form. In our Gastroenterology Collaborative Group, we have had a similar problem with follow-up flexible sigmoidoscopy in the treatment of ulcerative colitis. In spite of signing a consent form and agreeing ahead of time to the procedure, both physicians and parents often refused (11). The results in both cases were influenced by these protocol violations, although the basic studies still had validity in all other respects.

Participating centers must be screened carefully to be sure they can comply with the protocol and recruit the patients needed. It is important to be sure that collaborating centers have no commitments to conflicting protocols and that they have the resources to recruit patients and keep up with the paperwork. Conflicting studies will decrease the number of patients enrolled and may bias the results, depending on how patients are randomized. If the research staff does not have time to recruit patients into multiple studies, patients may never hear about the study, or record keeping may suffer.

HOW MANY CENTERS ARE NEEDED?

The number of centers to include in a collaborative study is always a major question. More centers should mean a study should get done more quickly. The problems that arise in recruiting a larger number of centers are the significant increase in workload and the increased cost in terms of overheads, travel, and monitoring. The more centers involved, the more difficulties arise in monitoring quality and in promotion of the study to keep investigators committed.

In choosing sites for a collaborative trial, the principal investigator and sponsor must be sure each potential participant understands the minimum number of patients expected and the time period for enrollment. If some sites do not perform well and
only enter an occasional patient, the final patient sample may be very unrepresentative, and the results less significant. When centers are slow to enroll patients and a study is extended, there is a much greater chance for bias (12). This is especially true if the study is extended beyond 3 or 4 years. Patients entered early may not be the same as patients entered late, or methods of enrollment may vary as personnel change. New drugs or formulas may alter the patients who can be used for a trial. If the investigators’ preferences change, there may be more and more reluctance to continue the study. Adding extra centers to make up for any underperforming centers might be helpful, but the best choice is to pick centers with a high probability of success.

REASONS FOR PARTICIPATION

There are many reasons why investigators might be interested in joining a multicenter trial, but a few of the more important include: (a) a high scientific or clinical interest; (b) the study product having the potential for significant benefits to patients; (c) possible benefits of academic prestige for individuals belonging to the group doing the study or of additional patients to the center; if the group is small authorship and publication; and funding from the study, which may allow support for other activities or provide a significant honorarium for the investigator.

A high degree of scientific interest and potential patient benefit have been the major stimuli for our Pediatric Gastroenterology Collaborative Group to work together and develop research protocols. To maximize this interest, all members are involved in the planning of protocols. This allows each investigator to take some ownership in the protocol and helps maintain a high level of interest throughout the study. It also gives an opportunity to discover potential problems with a protocol early on: Is it too complicated? Does it vary from standard practice? Is it uninteresting? Is there too much paperwork or high risk? Are there enough patients? If these issues are not addressed at the very beginning, it may be difficult to find collaborators, and the success of the study may be in jeopardy before it ever starts.

Benefits for patients can be a good motivation for participation in multicenter trials, especially if a new product has consumer interest, potential significant improvement over existing treatment, or fewer side effects. If new products are minimally different, patients may not see much benefit in participating, and it may be hard to motivate investigators. Ideas that are too new or radical may also meet with some resistance from physicians. In a recent protocol review of a new elemental formula, the investigators expressed much concern because there were too many changes in the formula. Although patients might benefit, no one could figure out how to analyze the results in terms of what new ingredient might make a difference. The scientific interest was in more thorough testing of the individual additives before combining them into one “super” formula.

In small collaborative group studies, coauthorship and the right to claim membership in a group or study may be important. Authorship and publication rights should
be established early on in discussions among collaborators and between collaborators and sponsors. Who will write the paper? Who will be the first author, and in what order will investigators be listed? It is also critical to clarify all issues regarding ownership and analysis of data. Investigators and sponsors need to understand who is responsible for what in the interpretation, presentation, and publication of data.

**PROTOCOL DEVELOPMENT, COORDINATION, AND MONITORING**

Most of the physicians in our collaborative group like to develop a protocol independently, or in cooperation with a sponsor. They also like to analyze data separately. The general feeling is that a protocol written by an investigator will be less biased and will carry more weight academically. Whether a protocol is developed by an investigator or is company sponsored, there is an advantage in having potential collaborators meet early on during the planning stage. Advice and input from potential collaborators helps build a real partnership between the sponsor and the investigators. Nurturing this partnership to the advantage of both sides gives a protocol the best chance for success.

In those cases where there is an interest in approval from the Food and Drug Administration or other regulatory agencies, the quality of safety and efficacy data are the top priority. We have found it useful to meet the appropriate section of the FDA in planning pediatric drug studies where we would like to see a drug approved for pediatric use. Although working with the FDA in protocol development is no guarantee that the results will lead to agency approval, at least all of the data considered useful are planned for ahead of time. Unfortunately, rules often change, so that even the most careful planning may not lead to the anticipated approval.

In designing a protocol, it is important to collect an adequate amount of information, but too much data discourages investigators and consumes too much time. There is always a concern among investigators that data not collected might lead to some important opportunity being missed. On the other hand, narrowing the scope of a study is often more realistic when it comes to protocol compliance and getting a study done. Trying to balance the right amount of scientific data without missing important information is critical to the success of any study. This may become an even greater problem with the increasing emphasis on data regarding cost analysis, functional status, and quality of life. All of these issues are important, and we will need to find the appropriate tools and develop the methodology in pediatrics to incorporate these data without overburdening our collaborative research efforts.

When individual investigators come together to collaborate, a single institution must become the coordinating center and be responsible for all aspects of the study. This is a great responsibility and requires adequate staff and the time commitment to keep the study moving. The principal investigator must take the lead to interest other collaborators, organize pretrial meetings and follow-up, and provide ongoing motivation for participants. In our Gastroenterology Collaboration Group, my center in Houston has been the coordinating center for all of our protocols, but we have
encouraged different members to act as principal investigators for different studies. This has created some confusion with sponsors, especially in terms of funding. In one instance, we split a percentage of funds between the coordinating center and the principal investigator's institution. The contract for this type of arrangement was difficult to write, but the split funding provided real benefits academically to the principal investigator. At the same time, it allowed our coordinating center to handle the data, monitor the study, and support the principal investigator.

It is critical that each center have a coordinator who will take responsibility for the study. Enrolling patients and completing data collection forms is time-consuming, and most physicians are too busy to guarantee daily attention to a study protocol. It is helpful if the coordinator has some experience in clinical trials, but if not, a pretrial meeting to review the protocol is essential to help the coordinators and the investigators understand their responsibilities.

For large multicenter trials, monitoring of study sites and data is the key to running a high-quality study. This requires careful planning as to what will be monitored and who will do the monitoring. Will it be done on site or from a distance, and how often will data be evaluated? Monitors must promote enrollment, check for accuracy of records, ensure that adequate personnel are present in each center, determine if the protocol is being followed as written, and look at all adverse reactions and their appropriate reporting. Failure in any of these areas can lead to serious quality issues that will undermine a good study.

Because of expense and training and time commitments, our collaborative group has depended on telephone monitoring and careful review of data collection forms for all of our studies. This is not ideal, but it has been difficult to find funding for on-site visits for the protocols we have written. In the future, we would prefer on-site monitoring to check for accuracy of data collection and adherence to protocols. In addition, on-site visits will give us a better opportunity to stimulate continued interest and patient enrollment.

Finally, we have found that an advisory board can be of help in evaluating the progress of a study. We have a pediatric gastroenterologist, someone trained in clinical trials, and a pediatrician to monitor results. This group has the authority to stop a trial if there is any problem regarding safety and efficacy. They can also do an interim analysis to see if data suggest a study should continue or be terminated for any other reason. We are also considering a steering committee for future studies. This group would include study investigators from different regions so that they can work with centers that are geographically close. Their role will be to promote the study, maintain enthusiasm, and help with any recruiting problems.

SUMMARY

Once a decision is made that a multicenter clinical trial is desirable, various questions should be addressed before starting. How many centers will be needed? What setting will work best? How many patients must each center recruit? Is the
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protocol of sufficient interest to attract other investigators? Do potential collaborating centers have appropriate patients in appropriate numbers? How long will it take to get the study done? Who will serve as principal investigator? What about publication rights and authorship? How will the study be monitored? How much data is absolutely necessary to answer the question? Once these issues are addressed, the sponsor and investigators can begin the task of picking the collaborators and progressing to a successful conclusion.

REFERENCES


DISCUSSION

Dr. Perman: What are your thoughts about incentives for individuals to participate in multicenter studies? Clinical investigators are committed to producing new knowledge, and that is, and probably should be, reward in itself. But the reality is that publications arising from multicenter studies are simply not given the same kind of recognition as work that reflects the creativity of the individual investigator. So what have you done to allow the recognition of individual participation in a study while at the same time asking individuals to work as a group?

Dr. Ferry: The main thing that we have done is to have our group very involved in protocol development. We also insisted that someone from our group be a principal investigator for the protocol, even if the project originates from the industry. That usually works well, though not in every instance—it depends on the goals of the particular study. We have tried to spread around our authorship to help younger investigators. This gives them a chance to be involved in one or more publications through participation in a multicenter study.
Dr. Hamburger: There could be 13 authors?

Dr. Ferry: We do not all participate in every study, but, in fact, we have had 13 authors. That certainly dilutes the recognition, but in talking to some of the young investigators, they feel their participation has been helpful to them in their own academic promotions. Another incentive is the need of investigators for more help. In doing multicenter studies, a big motivator is funding for a coordinator or research nurse. We have tried to provide some funding to allow for a proportion of someone's time for each study.

Dr. Lucas: You touched on the question of what you mean by a "clinical investigator." We have done about 15 large-scale multicenter trials now in infant nutrition, and we have tried very hard to achieve 100% follow-up or near to that, with very little loss of data. The only way that has been possible is by not relying on clinicians to do anything at all. We rely on clinical investigators to be part of the intellectual process, but we don't rely on them in any other way—either clinical nurses or medics—to collect data or do anything practical in the study, because they are always too busy, and indeed they should put their clinical responsibility before their research responsibility. So we have found that the only way to run big clinical trials is for them to be fully staffed with totally committed staff. Obviously, when the results come out, we can decide how the publications are going to be divided among investigators, and so on. But I am interested that you actually manage to get clinicians to do effective work reliably in multicenter trials.

Dr. Ferry: We do have our problems, and we have had some major protocol difficulties—as an example, one of our studies required an invasive procedure as a follow-up. We could hardly get any of the investigators to do the follow-up or get the parents' permission. So we do have difficulties that we have not solved. However, we do not expect our investigators to actually do very much of the work, and we communicate mostly with the coordinator or research person. The clinical investigators have to be committed though; if they are not enthusiastic, you won't get the patients.

Dr. Steenhout: I think it is true that some investigators don't always read the protocol, but in multicenter trials, it is also the responsibility of the principal investigator to check that the others have really understood and read the protocol. With regard to data storage, I agree with Alan Lucas that it must be the same group or person who inputs the data into the data base to ensure that it is done in the same way throughout and to minimize problems during the statistical analysis. My question is about the statistical aspects of such big trials, because clearly, your cases are different from center to center, and the way people work is different. What must we do when we design a protocol for such a trial to avoid too many differences between centers and ensure that we don't introduce too much bias?

Dr. Ferry: I am not sure I have an answer to this question. We work with academic and nonacademic centers. We picked the centers in that way hoping that the studies would thus gain in generalizability, at least in the respect that the patients and clinicians come from many different areas of the United States and Canada. But the centers are truly quite different, and in any given study, there may be certain centers that fail to produce any data. For example, one of our centers is such a large referral center that they see mostly very complex patients who rarely fit our studies. So the only way you can deal with that is to ask the right questions about each group ahead of time and then make a decision as to whether you do truly want similar centers or whether you want a variety. Sometimes, it is better to be different than to be the same.

Dr. Berlin: If we are talking about randomized trials, I think most people would agree that randomization would need to take place within a center, so that you are stratifying everything else, and whatever clinical variability there is is controlled for. You then have
unconfounded treatment in the center and in theory, at least adjustment for centers is probably not going to make much difference. Once you move away from randomized trials, things are much messier, and that is the next 6 months of a statistics course.

*Dr. Whitehead:* You emphasized the great importance of the study coordinator. Could you spell out what you think are the key attributes of such a person?

*Dr. Ferry:* The ideal is someone who has had experience in doing clinical studies and understands the importance of accurate data collection. Such people are not easy to find, however, because personnel come and go. We are constantly training new people. A very important quality is organizing ability, particularly attention to detail, so that the person recognizes when information is missing and knows how to go out and obtain it before that patient is lost because of missing data. I also think good communication skills are important. Your success in getting patients to participate and keeping them in the study really depends to a large extent on the coordinator’s good relationship with patients.

*Dr. Lentze:* I was interested about your comment about disease-specific data bases. I think this is very important, and we all want them. But how do you assess that the data base is fueled by the centers? We had faced this problem with diabetes and cystic fibrosis, and the data bases are only theoretical because they are not properly fueled. In theory, it is wonderful, but in practice, people don’t provide the data. How do you overcome this problem?

*Dr. Ferry:* We use a common outpatient visit form to collect the same data. It is a checkoff sheet that can be used for data entry. What we don’t have is every blank on the page filled in as we would like, and I think it is going to take some time to convince people that when something is missing, we really have a problem. However, one of the advantages of using this form is that at least everyone is gathering most of the same data in the same way in the clinic setting.

*Dr. Aggett:* Can I ask you about your experience and practice in ensuring good quality control when it comes not only to the collection of data but also to the methods that are applied if there are serial measurements and, of course, also laboratory measurements?

*Dr. Ferry:* In terms of clinical measurements, some of our studies have been following growth in inflammatory bowel disease, and here, we have requested that each of our centers must use a stadiometer, and they must average more than one measurement. We do try to standardize as much as we can. In terms of laboratory work, we haven’t done studies where this has been very critical. What we have found is that the cost of doing such studies is enormous at most hospitals and academic centers, but we haven’t been involved in the kind of study where you have to have very highly trained laboratory personnel to do specific tests.

*Dr. Rey:* I am puzzled by your presentation. You presented all the difficulties that can arise in multicenter trials, but at the end, I had the feeling that there was no pilot in the plane! Can you give us an example of one of your studies that was well done with a simple answer to a simple question? I can give you an example of the reverse: a very famous study in the United States—the PKU collaborative study, involving at least 30 centers. There were two steps: the first was to determine the IQ of the patients at 4 years of age—the answer was clear, the IQ was around 100; the second was to compare two treatment groups, one treated with a phenylalanine level between 1 and 5 mg per 100 ml, and the other between 5 and 10. After a few months, it was apparent that there was no difference in the dietary score index between the two groups, so it was impossible to answer the question (1). But the principal coordinator continues to cross the world every year to present data—not on the IQ of the two treatment groups but on the consequences of the loss of dietary control, which is a completely different question from the initial one. So he is giving a false response to a true question, and I find myself asking whether there is really a place for multicenter trials in gastroenterology.
Dr. Ferry: What I tried to do today was to give an overview, both from the sponsors' and from the investigators' side, on how to attract the right people to do studies, and what you should be looking for in coordination and data gathering. One of our first studies was a drug study in inflammatory bowel disease involving one of the newer 5-aminosalicylic acid drugs. There was great interest in the pediatric gastroenterologic community about whether this drug was as good as existing treatments, so we decided to do a comparative study. We hypothesized that there shouldn't be very much difference in response, so what we looked at was whether this drug had fewer side effects. Our group of investigators met together, made an assessment of how many patients might be available, and began to develop a protocol and criteria for the kinds of patients to include. We did our statistics ahead of time and knew what sample size was needed; we built in an interim analysis to look at the study as it went along; we had an advisory group to look over our shoulder and make sure that we weren't causing any problems for the patients; and we structured the study so that it could be done in 2 years. Each participating center signed a letter of intent and named a study coordinator. As the study progressed, the enrollment rate was slower than we had wanted, but we did get to a point toward the end of the 2 years when we had enough patients to look at the safety issues. It turned out that the new drug wasn't nearly as effective as the comparison drug, and we decided to stop the study. In all multicenter studies, you have to do the following: develop an interesting and valuable protocol, share it with all investigators for their input, determine whether it is feasible, determine whether there will be enough centers and patients, set the inclusion and exclusion criteria firmly, but not so strictly that you can't find the patients, and establish your statistics and questions ahead of time. Once you get into the study, you must carefully monitor all the data and constantly encourage centers to actually enroll patients.

Dr. Walter: We have done a number of multicenter trials in childhood development, and we have had to involve centers for whom research is not part of their culture. They are providing important clinical services, but they are not routinely involved in research. So, like you, we have had to invest very heavily in research coordinators to make sure the data are being collected appropriately and in a consistent manner. I was, therefore, a little surprised to hear you say that you thought the quality of data would go up when you add centers to a trial. In our experience, it is very difficult to maintain the quality under these circumstances because of the diversity of situations in which people work. It can be done, but it takes a great deal of continuing effort during the life of the trial. My second comment relates to the point that Dr. Berlin made about center-by-treatment interactions. And this is a very controversial problem in the analysis of multicenter trials. Quite apart from the statistical strategy that you might use for the analysis, our experience has often been that as a reward for taking part in a multicenter study, individuals are often interested to know if their center is doing better or worse than average. There is an expectation that there will be center-level results provided to them, and you have to be very careful to explain that that is a dangerous path to go down because of the obvious difficulties in looking at relatively small subgroups. An extreme case of that is in the situation where the trial comes out with essentially negative results, or no difference between interventions. We had that experience a few years ago, where a surgical trial showed that a particular intervention is not really beneficial, but there was serious income involved on the part of the surgeons, so all sorts of cases were made to us to try to persuade us to consider exceptional subgroups, and often their centers, in particular, where their patients would do better.

Dr. Ferry: Large multicenter studies provide greater generalizability of data, but in fact, monitoring is more difficult, and quality may be an issue. We do try to have enough subjects in each center so that there can at least be some randomization within the center itself. If we
can get a center to enroll six patients over a year or a year and a half, we are very happy with that; it is the center that enrolls only one patient that creates difficulties with data.

Dr. Tsang: The question of creativity in multicenter trials is a real one. We are involved in multicenter trials with NIH in regard to intensive care units. One of the things we noticed very quickly was that the investigators became very uncreative. Most of the questions have already really been asked, and the multicenter trial is more of a confirmatory study than anything else, so the investigators quickly got bored because they all had to agree to a very common protocol, which was rather bland. The other investigators in the institution were also turned off because they felt that this was only a data-collecting exercise, and there was no creativity. The real problem is for young investigators: young people get really put off because they are participating in a study with no hope of academic recognition or advancement, and no input from them. For example, when multicenter trials first started to be done, the NIH had very strict criteria that ensured that the minor people had no input and were never invited to participate at the planning stage. I think this is a real problem that needs to be tackled, especially as we are about to train new investigators, and we want to get clinical investigators excited about the investigations, young investigators especially. So a balance has to be found between trying to establish enough data, enough data bases, statistics, etc., and allowing a reasonable amount of creativity. Tag-on studies are one way to do this, but we must encourage the drive that drove us into clinical investigation.

REFERENCE