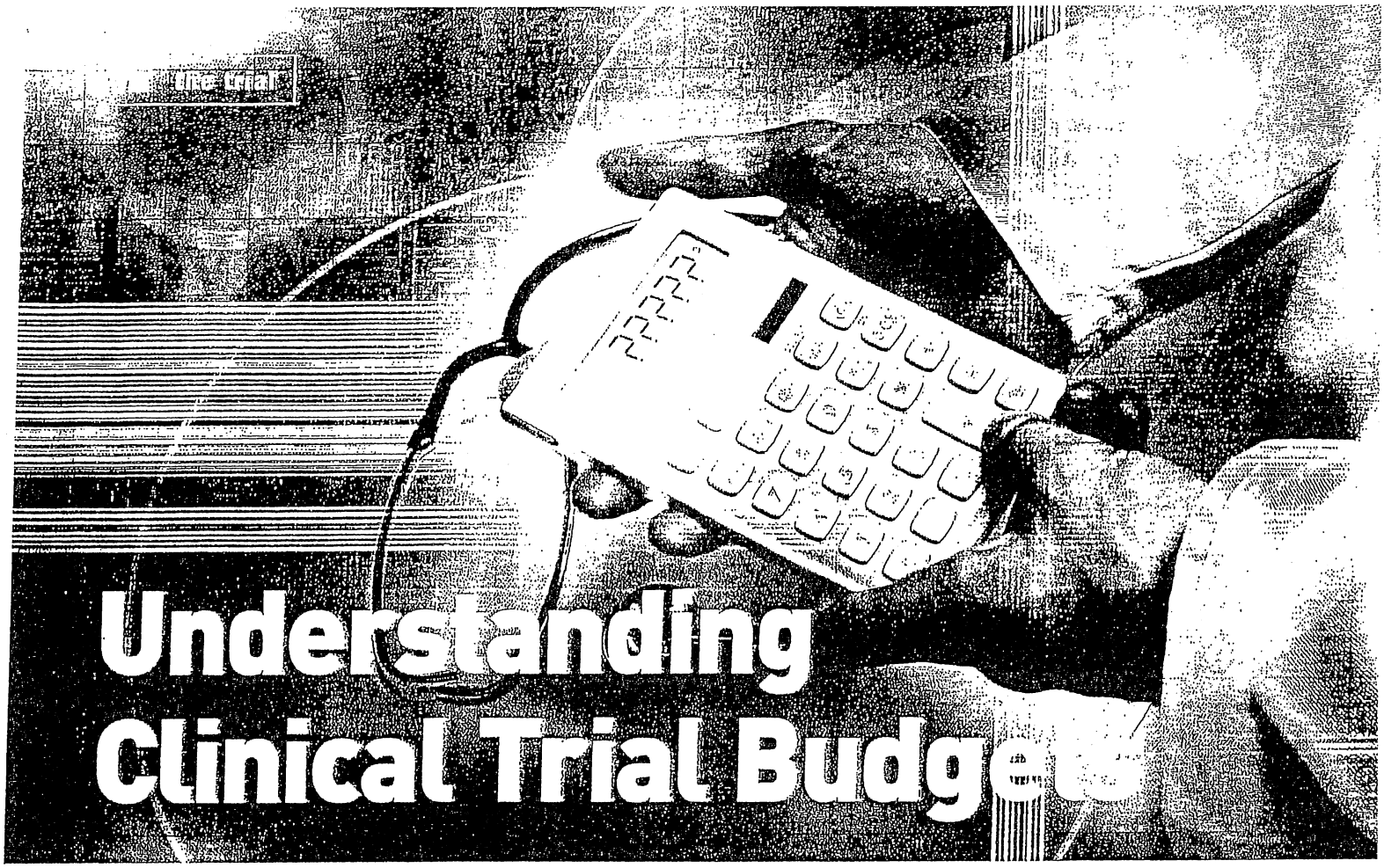

Understanding Clinical Trial Budgets

Industry and research sites have always enjoyed a symbiotic relationship. Industry needs research sites to conduct high-quality research; research sites need industry to assist in the advancement of medical knowledge. Randomized clinical trials and their developing methodology have had a substantial impact on the advancement of medical practice [1]. With increasing financial demands on research sites to remain profitable, the financial manager at the site must be able to religiously examine all of the costs involved in conducting a study and negotiate adequate compensation for work performed. This article provides insights into building an accurate and adequate study budget for research sites and industry, and identifies additional reimbursement considerations associated with investigational device trials. It also describes realistic payment structures and budget negotiation techniques that can be used to assist parties during the budgeting process. (*Clinical Researcher* 2003;3(2):12–7.)

Building a budget based on total project cost

When developing a budget, the research site must analyze the protocol not only scientifically but also financially. However, the research site should not make the mistake of including only the obvious direct study costs, which are the total charges to the sponsor for all of the line items listed in the budget. Many other expenses need to be considered when determining the total cost to the site of participating in the research study, including start-up costs, operational costs, hidden costs, screen failures and indirect costs. Start-up costs and general overheads can account for up to 53% of the total project costs [2].

Start-up costs

Start-up costs at larger research sites can average US$ 5000 or more per protocol. These costs consist of the effort required by study coordinators and physicians to move the protocol through the submission and approval process. At most sites, a departmental research committee must review and approve protocols with more than minimal risk prior to the institutional review board (IRB) review. This preliminary review generally involves the efforts of several physicians and administrative personnel. In addition, the study coordinator(s) and/or principal investigator(s) expend effort on

such activities as reviewing the protocol, drafting the consent form, identifying budget costs, summarizing information for the departmental research committee and IRB review of the protocol, and preparing study billing cards. Pharmacy personnel should also complete a review of the protocol and provide a cost estimate for pharmacy services. The IRB must then review and approve the research protocol to ensure the protection of the rights and well-being of potential research subjects. The costs associated with these processes usually occur prior to the signing of the clinical trial agreement and need to be recognized as true study costs.

In addition, there are study start-up costs that occur after the agreement is finalized. Equipment, supplies, devices/drugs and placebos need to be ordered, appointments arranged and personnel trained. Screening costs, as well as time and travel for participation in investigator meetings, also need to be considered when preparing the budget.

Operational costs

Operational costs encompass a large array of expenses and can be separated into subcategories such as personnel, patient care, equipment, supplies, travel and one-time fees. In addition, for items that do not specifically tie into another category—e.g. patient remuneration, publication costs and pharmacy dispensing fees—an 'other' category can be incorporated.

Personnel

Adequate compensation for personnel is essential to the success of any research study. The total salary compensation includes salary plus any fringe benefits. Therefore, when budgeting for salaries it is crucial to incorporate fringe benefits and anticipated fiscal year salary increases [3]. It is also important to be consistent in the way that compensation for personnel is computed. For example, salaries are usually calculated as a percentage of time over 12 months since a person may work on more than one trial at the same time, and therefore a proportion of their time is charged to each of the trials that they work on. The research site may want to establish standard rates for various classifications of employees that can be used when budgeting. If the principal investigator or any of the other study personnel have to travel to the sponsor's site, then airfare, car rental, gas, parking fees, lodging, a daily allowance and other travel-related expenses should be included in the budget. Personnel time also needs to be considered when travel is required for the study.

Start-up costs at larger research sites can average US$ 5000 or more per protocol and consist of the effort required to move the protocol through the submission and approval process

Patient care

Patient care costs need to be carefully selected to ensure that the correct procedure, test or service is identified in the budget and that all of the associated costs, such as supplies, drugs and facility fees, are included as a line item. If study-related procedures are misidentified or missed completely, the institution could lose money. The American Medical Association's Current Procedural Terminology (CPT) code is the most widely accepted nomenclature for the reporting of physician procedures and services under government and private health insurance programs. CPT codes provide a uniform language that can accurately describe medical, surgical and diagnostic services, and they provide a reliable nationwide means of communication among physicians, industry, patients and third parties [4].

Patient care costs need to be carefully selected to ensure that the correct procedure, test or service is identified in the budget

Standard of care (SOC) patient care costs are the tests, procedures and services that

Carol McAlister[1] and Virginia (Nickie) M Bruce[2]
[1]Mayo Clinic and [2]Mayo Foundation, MN, USA

Carol McAlister is an industry financial specialist within the Department of Research Administrative Services of Mayo Clinic in Rochester, MN, USA. Along with the other industry financial specialists in her department, she is responsible for research studies from concept to closure, developing study-specific budgets; reviewing sponsors' proposed budgets; negotiating mutually satisfactory financial agreements; reviewing and negotiating payment terms; performing invoicing and collections duties; and carrying out study closure obligations. Ms McAlister has an MSc in telecommunications and an MA in health and human services administration from St Mary's University, MN, USA. She has worked as an industry financial specialist since 1998. Prior to this, she has previously been a research technologist at Mayo Clinic, Rochester and an assistant administrative director for Wolff Laboratories, Inc., IA, USA.

Nickie Bruce is a contract administrator within Mayo Legal Contract Administration (LCA), a newly developed unit within the Legal Department of Mayo Foundation in Rochester, MN, USA. She supervises six contract managers and eight secretarial support staff. The LCA is responsible for developing, reviewing and negotiating material transfer agreements, research, consulting and Mayo Clinical Trial Services (MCTS) contracts, and provides support for these contract activities for all Mayo entities. She has a BS from Winona State University, MN, USA. Previously she worked as a paralegal in Mayo Foundation's Legal Department from 1992–1995, a contract manager for the Mayo Foundation from 1995–2000 and a contract manager for MCTS from 2000–2002.

research subjects would have had to pay for were they not participating in a research study. A patient's insurance company typically pays these costs. All patient care costs that are not SOC should be itemized in the study budget. Most institutions offer discounted rates, known as research charges, on patient services performed for research purposes.

Equipment and supplies

Equipment is generally considered to cover items that cost more than US$ 1000 and that are estimated to last at least 2 years. It is recommended that service and maintenance contracts for equipment be included in the budget. Unless the equipment is restricted, the research site can usually retain the equipment at the conclusion of the study [3]. If the equipment has to be returned to the sponsor, it is suggested that the expense for sending it back be included in the budget. In contrast, supplies are considered to be expendables valued at less than US$ 1000 and are not expected to last more than 1 year.

Investigational device concerns and their effect on the budget

Studies involving investigational devices have reimbursement concerns that need to be addressed prior to finalizing the study budget. On November 1, 1995, Medicare coverage was expanded to include certain medical devices not yet approved for marketing but that are being studied by a US Food and Drug Administration (FDA)-approved clinical trial [6]. The FDA's investigational device exemptions (IDEs) define two categories of devices used in clinical trials:

Category A (experimental) - Category A devices are not covered by Medicare. These are considered to be innovative devices for which the 'absolute risk' of the device type has not been established and initial questions of safety and effectiveness have not been resolved [6]. Therefore, the FDA is unsure of whether these device types can be considered to be safe and effective. All costs associated with the placement of a Category A device need to be incorporated in the study budget.

Category B (non-experimental and investigational) - Category B devices are newer generations of proven technologies for which initial questions of safety and effectiveness have been resolved. Devices placed in this category are considered to represent evolutionary changes in proven technologies and are viewed as potentially reasonable and necessary by Medicare, thus opening the door for coverage [6]. However, payment for Category B devices and related medical care is not guaranteed, so a decision on Medicare coverage should be sought before the budget is finalized.

To determine whether coverage for a Category B device can be expected from a third-party payer, specific information regarding the device can be sent to the research site's Medicare intermediary. The Medicare intermediary will review the device information and determine whether Medicare will cover the cost of the study device and any device-related procedures. Generally, if Medicare is likely to deny coverage, then so will private insurance companies. This is crucial information that must be available prior to finalizing the study budget. When taking part in clinical trials involving devices, the research site should pursue negotiation of appropriate 'denied claims' language in the clinical trial agreement. Thus, if Medicare or private insurance denies a claim because the device is deemed experimental in nature, the sponsor will be responsible for the claim instead of the patient or the research site. However, it is imperative for the research site to read the denied claims language carefully, noting whether the sponsor will pay the denied claim in full or only in part. If the sponsor will pay for only a portion of the cost of the denied claim, it is wise to obtain an estimate of the cost of the medical care outlined in the protocol in order to evaluate the financial risk to the research site if the claim is denied.

Unanticipated expenses are difficult to adequately budget for. Hidden costs can reduce the potential revenue derived from a study and impair the site's ability to cover the payroll

It is imperative for the research site to read the denied claims language carefully, noting whether the sponsor will pay the denied claim in full or only in part

One-time charges

One-time charges are costs that the sponsor must pay regardless of how many subjects enter the study. Some examples include initial IRB fees, IRB annual continuation fees, pharmacy administration fees and protocol administration fees.

Hidden costs

There are many hidden costs associated with site participation in a research study. Unanticipated expenses are difficult to adequately budget for. The following are some commonly encountered sources of expenditure that should be considered when reviewing the study protocol:

- Advertisements
- Study subject parking
- Study subject meals
- Study subject travel
- Pharmacy charges
- Record storage
- Mailing
- Shipping
- Dry ice for shipping laboratory specimens
- Screening
- Study subject dropouts
- Unscheduled events

Site visits by study monitors, adverse-event reporting to the IRB, resolving data queries and remote data entry are also hidden costs as they require additional personnel effort. Hidden costs can reduce the potential revenue derived from the study and impair the site's ability to cover the payroll and to pay for other expenses.

Another item of concern is the cost of a governmental, regulatory or sponsor-related audit. Depending on the size of the study, the support costs for an audit can be substantial. The researcher is responsible for providing information to the auditor for review, and support staff typically need to be available to answer questions. Generally, no funding

is available in the budget to cover the required support, so it is wise to propose in the contract that the sponsor will reimburse the costs related to an audit.

Termination of the study is also an unpredictable, hidden cost. It is in the best interests of the site to add a cancellation fee to the budget to ensure adequate compensation in the event that the study is terminated early.

Screen failures

Prior to drafting a budget, the researcher needs to consider the criteria for patient enrollment carefully to determine whether the desired patient population is likely to be difficult to enroll at the site. Patients who are initially recruited to participate in a study and then fail their screening examination are very costly to a site, both in terms of screening expenses and lost revenue. Generally, sponsors will offer a minimal amount of reimbursement to sites for study subjects who fail their screening examination. To determine whether the sponsor's reimbursement is adequate, the site should itemize all screening tests, procedures and services required for each protocol, and budget enough personnel effort to cover the recruitment and education of the potential study subjects. The clinical trial agreement should be read carefully to ensure that the sponsor does not place a limit on the number of screen-failure reimbursements that they will compensate for. This issue will require negotiation if the site decides that the

Patients who are initially recruited to participate in a study and then fail their screening examination are very costly to a site, both in terms of screening expenses and lost revenue

Clinical trial budget checklist

The protocol must be analyzed from a financial as well as a scientific perspective. Issues to consider include:

Study design:

- Number of patients for enrollment
- Study length
- Is it a drug or device study (potential expense/risk associated with device project)?
  - Category A
  - Category B

Start-up costs:

- Study coordinator/physician effort
- Committee reviews
- IRB review
- Screening costs (itemize all screening tests, procedures and services)
- Investigator meeting attendance

Operational costs:

- Personnel—salary plus fringe benefits
  - Travel (airfare, car rental, fuel, parking fees, lodging, daily allowance, personnel time)
  - Other travel-related expenses
- Patient care costs (CPT codes)
  - Ensure that the correct procedure, test or service is budgeted for
  - Must include all associated costs—i.e. supplies, drugs, facility fees, etc.
- Equipment (generally considered to cost over US$ 1000 and estimated to last at least 2 years)
  - Maintenance costs
- Supplies (generally considered to be valued at less than US$ 1000 and expected to last no longer than 1 year)
- One-time fees
  - IRB fees
  - Pharmacy coordination fees
  - Administrative fees

Hidden costs:

- Patient remuneration
- Publication costs
- Pharmacy dispensing fees
- Advertisements
- Study subject meals, parking, travel
- Record storage
- Mailing costs
- Shipping costs
- Dry ice for shipping laboratory specimens
- Study participant dropout rates
- Site visits by study monitors
- Adverse-event reporting to the IRB
- Resolving data queries
- Remote data entry
- Governmental, regulatory/sponsor-related audits
- Early termination (cancellation fee?)

Screen failures:

- Itemize cost of screening tests, procedures and services
- Budget for personnel effort to cover recruitment/education of study participants

Indirect costs:

- General overheads—e.g. space, depreciation, operations, administration, site facilities, insurance

Identify appropriate payment structure:

- Initial administrative/IRB fee
- Milestones that correlate with the schedule of activities identified in the budget

Glossary

Balloon payment	=	A large payment typically made by the sponsor at the end of the study when all patients have completed all study requirements
Cancellation fee	=	A fee paid by the sponsor to the principal investigator and/or research site for resources used in a study that has been cancelled by the sponsor. Such fees should be described in the contract
Category A device	=	A device not covered by Medicare as the FDA is unsure of whether it can be considered to be safe and effective
Category B device	=	Devices that are newer generations of proven technologies, the costs of which may be covered by Medicare
Clinical trial agreement	=	A legal document that sets out the responsibilities and obligations of all parties involved with the clinical trial
Completed patient/subject	=	A subject who has completed a clinical trial. Each study defines completion as is appropriate to that study. The definition of 'completed' should be clear to the sponsor and research site, and should be specified in the research agreement. Payments to the research site depend on such definitions
Direct costs	=	The cost to the sponsor of each line item of the study budget
Equipment	=	Capital items are those that must be purchased in order for the research site to perform the study. These should be included in the study budget because the charge occurs regardless of the number of subjects enrolled in the study. If the sponsor purchases equipment, the research agreement should indicate where final ownership will reside
Final payment	=	The last payment from the sponsor to the research site. Requirements for the final payment should be specified in the research agreement
Indirect cost	=	A percentage of the direct costs that is used to cover the site's overheads
Initial payment	=	The first payment from the sponsor to the research site. Often the initial payment is a percentage of the total contract. If the site fails to enroll any patients and the sponsor terminates the study, the initial payment (minus any non-refundable fees) will need to be returned to the sponsor. Therefore, it is important to negotiate nonrefundable fees so that the site can cover the cost of the effort expended on getting the study up-and-running at the site. The amount and terms of the initial payment should be described by the research agreement
Line item	=	A research-related item listed in the study budget with its corresponding cost, e.g. travel, supplies, telephone costs, etc.
Payment terms	=	A clause in the contract that describes payments from the sponsor to the research site. This clause includes the schedule, amount and criteria for payment
Personnel benefits	=	A surcharge (usually a percentage) on salary that covers sick leave, vacation, unemployment insurance, medical insurance, etc. Benefits should be included when salaries are calculated in a budget
Personnel charge	=	Salary charges for the staff performing the clinical trial
Research charge	=	A reduced charge for a clinical procedure/laboratory for research studies, established by sites
Screen failure	=	A patient who has been screened for entrance into a clinical trial but who has failed to meet the inclusion criteria of the study
Supplies	=	Expendables valued at less than US$ 1000 and that are not expected to last more than 1 year
Unscheduled events	=	Medical procedures/laboratories that are not budgeted items but that occur as a consequence of a subject's participation in the clinical trial. These expenses are charged to the clinical trial account. The research agreement should describe the financial responsibility for these events. The consent form should reiterate the description that is in the research agreement

Indirect rates vary among organizations. For example, universities have overhead costs ranging from 20–40%, which is generally higher than independent research centers

sponsor's proposed reimbursement for screen failures is inadequate.

Indirect costs (overheads)

Indirect costs are a percentage of the direct charges that are used to cover the non-line-item charges of the research site. Indirect expenses are associated with every research study and should be considered to be valid project costs. Some common indirect allocations include cost of space, depreciation, operating the facility, administration, accounting, utilities, telephone service, library, computer networks, custodial service, insurance and security.

Indirect rates vary among organizations. For example, universities have overhead costs ranging from 20–40%, which is generally higher than independent research centers [5]. Larger organizations negotiate their indirect rate with the Federal government. The negotiated indirect rate is dependent on the number of ongoing research studies at that particular organization [3]. In general, laboratory-based research studies have a higher indirect rate than clinic-based research studies because equipment must be purchased and its depreciation in value must be taken into account.

Budget negotiation

It is important to consider the big picture when negotiating a research budget. The research site must be clear about its goals for both the immediate and long-term future. Pushing for maximum compensation from the study sponsor may accomplish immediate goals but it may cost subsequent studies with that sponsor. In contrast, negotiating a reasonable study budget may result in the creation of a long-term relationship with that sponsor.

Most sponsors provide the potential research site with a sample budget based on their continual exposure to, and experience

of, research costs [5]. However, budgets proposed by the sponsor generally contain some degree of flexibility. If the proposed budget is not sufficient to compensate the research site for its involvement in the study, the site should request additional funds and provide the sponsor with a solid rationale for the requested increase. To lessen the chance of confusion or miscommunication, it is best if only one individual from the research site, such as the site's financial manager, negotiates the budget with the sponsor.

Communication is crucial for successful negotiation. When underlying concerns are effectively communicated, both parties are better able to work together to find solutions. Since most negotiations are done by telephone, it is difficult to envision the people with whom you are negotiating. First impressions are generally lasting, so friendliness and a gracious tone can be an important investment in the negotiation process [5].

The dynamics of a study can also affect the negotiation process. For example, a researcher or financial manager who learns that the sponsor is having trouble recruiting sites may be at an advantage when requesting additional funding [5]. On the other hand, the same site may be at a disadvantage in terms of acquiring additional funding if the researcher or financial manager learns that the sponsor is turning down sites because of the demand. Other helpful information might include the total budget allocated to each aspect of the study, the amount of latitude available to expand the funding at each site, the overall financial pressures the sponsor is experiencing and how important the sponsor thinks it is to include a particular site or researcher in the study [5].

Researchers and financial managers must decide which clinical trials are cost-effective to conduct and how much financial room there is to compromise with the sponsor.

Researchers and financial managers must decide which clinical trials are cost-effective to conduct and how much financial room there is to compromise with the sponsor

A compromise might entail discounts, line-item reductions or personnel reductions in the site budget. The compromises selected are limited only by the imagination of the parties involved [5].

If the negotiation process comes to a standstill and the two parties have distant opinions, the researcher can decline the opportunity to participate in the study. Only the site can determine whether it is fiscally prudent to participate in a study where it will lose money.

Realistic payment structure

Once the research site and sponsor have agreed on a budget, the next step is to design an adequate payment schedule for work completed. Cash flow is a consideration for most research sites. The site needs to be thoroughly aware of how the milestone payments correlate to the schedule of activities required by the study. Payments based on the number of patients who complete the study may result in financial stress for a site as it waits for a balloon payment that might take 6–9 months to obtain [5]. It might be more favorable to organize payments to coincide with the completion of a visit or a procedure. It is important for a site to discuss its situation with the sponsor and to negotiate milestones that are reasonable and equitable for both of the parties.

When negotiating a payment schedule, consideration should be given to obtaining a percentage of the total budget (perhaps 10%) on execution of the clinical trial agreement. This upfront payment can be used to cover study start-up expenses and improve cash flow. The research site should review the proposed payment schedule thoughtfully. If payment is dependent on an action being completed within a certain timeframe—such as the sponsor's receipt of case report forms—it is important to determine whether the timeframe specified in the payment schedule is reasonable. The payment schedule should be evenly spaced, with no large balloon payment scheduled for the end of the study. By asking for funding to commence on contract execution, one-time fees, non-refundable start-up costs and upfront funding associated with study patients will help to pay for some of the study costs until the actual study milestones are achieved and payment is received.

Cash flow is a consideration—the site needs to be thoroughly aware of how the milestone payments correlate to the schedule of activities required by the study

Conclusion

In order to develop an accurate and adequate clinical trial budget, it is essential for the research site to have a good understanding of the study protocol. A thorough evaluation of all the costs associated with study conduct can then be made so that adequate compensation can be negotiated. Device studies present additional reimbursement concerns that should be addressed before finalizing the study budget. In addition to the budget, it is also important for the study's payment schedule to be designed in a reasonable manner based on the schedule of activities required by the study. Research sites are becoming more proactive and participatory when negotiating budgets with study sponsors. Effective communication between the research site and the study sponsor will assist both parties during the budgeting process and ensure more successful budget negotiation.

Contacts for correspondence:
Carol McAlister, MA, MSc. Tel: +1 507 266 0462,
Fax: +1 507 284 4288, E-mail: mcalister.carol@mayo.edu
Nickie M Bruce, BS. Tel: +1 507 266 4474,
Fax: +1 507 284 4183, E-mail: nbruce@mayo.edu

References
1. James KE. Health services clinical trials: Design, conduct, and cost methodology. *Control Clin Trials* 1998;19:131–3.
2. West DA, West TD. Financial managers' costing expertise is needed in clinical trials. *J Health Care Finance* 2000;27:11–20.
3. Ellett ML. Budget for a research proposal. *Gastroenterol Nurs* 1993;15:205–7.
4. American Medical Association. *Current Procedural Terminology 2003*. Chicago (IL): AMA Press, 2002.
5. Barnuff B. Negotiating budgets: Insights from your CRO/sponsor. *Res Pract* 2001;2(2):68–73.
6. The Medicare A Communicator—Special Supplement. St Paul (MN): Medicare Part A Office; Aug 1996. General Series Special Supplement No. 20.