Chapter 5

Design Decisions

FROM THE OUTSET OF THE STUDY, we are confronted with the need to make a large number of decisions, including, not least, "should the study be performed?" A clinical trial necessitates a large financial investment. Once we launch the trials, we can plan on tying up both our investment and the work product of several dozen individuals for at least the next two to six years. Planning pays.

Seven major design decisions that must and should be made before the trials begin are covered in the present chapter:

1. **Should the study be performed?**
2. **What are the study's objectives?**
3. **What are the primary and secondary response variables?**
4. **How will the quality of the information be assured?**
5. **What types of subjects will be included in the study?**
6. **What is the time line of the study?**
7. **How will the study be terminated?**

Five somewhat more technical design decisions are covered in the chapter following:

1. **What experimental design will be utilized?**
2. **What baseline measurements will be made on each patient?**
3. **Will it be a single-blind or a double-blind study?**
4. **What sample size is necessary to detect the effect?**
5. **How many examination sites will we need?**

PRE-DESIGN CHECKLIST

Before you can begin full-scale clinical trials, you need to establish:

- Mutagenicity, carcinogenicity, and toxicity in animals
- Mechanism of action in humans
- Maximum tolerated dose
- Minimum effective dose

We deal in Chapter 7 with the large number of minor details that must be thought through before we can conclude our preparations.

SHOULD THE STUDY BE PERFORMED?

We should always hesitate to undertake extensive trials when a surgical procedure is still in the experimental stages, or when the cross-effects with other commonly used drugs are not well understood. A cholesterol-lowering agent might well interfere with a beta blocker, for example.

If your study team is still uncertain about the intervention's mode of action, it may be advisable to defer full-scale trials till a year or so in the future and perform instead a trial of more limited scope with a smaller, more narrowly defined study population. For example, you might limit your trial to male nonsmokers between 20 and 40 who are not responding to current medications.

No full-scale long-term clinical trials of a drug should be attempted until you have first established both the maximum tolerable dose and the anticipated minimum effective dose. (In the United States, these are referred to as Phase I and Phase II clinical trials, respectively.) You should also have some ideas concerning the potential side effects.[10]

ONE TRIAL? OR MANY?

A single large-scale trial might appear more cost effective in the short term, says Michael Chernick of Novo Nordisk, but multiple tightly focused clinical trials generally are cleaner and faster. Multiple trials might be preferable in the following circumstances:

- Testing for different disease conditions
- Testing in different subpopulations
- Testing for different effects
- Monotherapy in one trial, combination therapy in another
- Different control groups for one-on-one comparisons for different benefits

The trials need not be concurrent and can often benefit from the results of other trials in their final design.

STUDY OBJECTIVES

I'm constantly amazed by the number of studies that proceed well into the clinical phase without any clear-cut statement of objectives. The executive committee has decreed "the intervention be taken to

[10]See Fazzari, Heller, and Scher (2000).

market" and this decree is passed down the chain of command without a single middle manager bothering or daring to give the decree a precise written form.

Begin by stating your principal hypothesis such as:

- **An increase in efficacy with no increase in side effects**
- **A decrease in side effects with no decline in efficacy**
- **No worse than but less costly and/or less invasive**

For Motrin™, for example, the principal hypothesis was that Motrin would provide the same anti-inflammatory effects as aspirin without the intestinal bleeding that so often accompanies continued aspirin use.

Keep the package insert in mind. For naproxen, another anti-inflammatory, the package insert reads: "In patients with osteo-arthritus, the therapeutic action of naproxin has been shown by a reduction in join pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.

"In clinical studies . . . naproxin has been shown to be comparable to aspirin and indomethacin . . . but the frequency and severity of the milder gastrointestinal adverse effects . . . and nervous system adverse effects were less in naproxin treated patients than in those treated with aspirin and indomethacin."

SET UP A DEFENSIVE TEAM

From the very start of the project, you need to establish a group whose primary purpose is to find the holes left in your design. I suggest a group rather than an individual because in today's corporate environment we all want to be thought of as team players. Moreover not everyone makes an effective critic. If you are managing several projects simultaneously, then the members of one study group may be called on to criticize the efforts of the other. Otherwise, and in particular if your firm is a small one, it may be best to call on external consultants. Of course, your own role should be that of a facilitator rather than a proponent of any specific point of view.

The objectives of your study should be stated as precisely as possible. Consider the following: "The purpose of this trial is to demonstrate that X763 is as effective as aspirin in treating stress-induced headaches and has fewer side effects."

Not very precise, is it? Here is a somewhat more informative alternative: "The purpose of this trial is to demonstrate that in treating stress-induced headaches in adults a five-grain tablet of X763 is as effective as two five-grain tablets of aspirin and has fewer side

effects." This is a marked improvement, though it is clear we still need to define what we mean by "effective."

A more general statement of objectives that may be used as template for your own studies takes the following form. "The purpose of this trial is to demonstrate that:

- **in treating conditions A, B, C**
- **with subjects having characteristics D, E, F**
- **an intervention of the form G**
- **is equivalent to/ as effective as/ as or more effective than an intervention of the form H**
- **and has fewer side effects."**

Again, we still need to define what we mean by "effective" and to list some if not all of the side effects we hope to diminish or eliminate.

PRIMARY END POINTS

Our next task is to determine the primary end points that will be used to assess efficacy. Here are a few guidelines:

- **Objective criteria are always preferable to subjective.**
- **True end points such as death or incidence of strokes should be employed rather than surrogate response variables such as tumor size or blood pressure. The latter is only appropriate (though not always avoidable) during the early stages of clinical investigation when trials are of short duration.**
- **The fewer the end points the better. A single primary end point is always to be preferred as it eliminates the possibility that different end points will point in different directions. On the other hand, as we will see in Chapter 14 on data analysis, sometimes more effective use of the data can be made using a constellation of well-defined results.**

The obvious exceptions are when (1) surrogate end points are employed and a change in a single factor would not be conclusive, (2) your marketing department hopes to make multiple claims, (3) competing products already make multiple claims.

The end point can be determined in two ways:

1. **Duration of the symptom or disease.**
2. **Severity of the symptom or disease at some fixed point after the start of treatment. This latter can be expressed either in terms of (a) a mean value or (b) the proportion of individuals in the study population whose severity lies below some predetermined fixed value.**

END POINT OR SURROGATE?

I'm taking drugs currently to control my blood pressure and to lower my cholesterol. Thus my interests will be served if my diastolic blood pressure remains below 90 and my cholesterol dips below 200. Or will they? As my passion for ice-cream reveals, I don't really care about cholesterol at all, or at least I didn't for most of my life. But I do not want to have a heart attack or a stroke and I've been told that if I keep my blood pressure down and my cholesterol levels low I may well avoid both.

It is both less time-consuming and less expensive to measure changes in surrogate variables like cholesterol and blood pressure than it is to track survival. The former can be detected in days to weeks; the latter will (hopefully in my case) take many years. But can we always be sure that the surrogate variable we measure is directly related to the end point that is our real interest?

Because very large-scale, very long-term clinical trials were conducted with government support, clinical trials employing surrogate variables such as cholesterol as end points are acceptable in some areas. But not in all. There are many documented reports of surrogate variables that have failed abysmally as predictors of sudden cardiac death (CAST, 1989), cancer survival (Fleming, 1995), or AIDS recovery (Fleming, 1995).

Any attempt to use a surrogate variable is sure to be viewed skeptically by the regulatory agency. It was not until well after the completion of LifeCore's clinical trials of its Intergel™ adhesion prevention solution, that adhesion was declared to be an end point rather than a surrogate.

On a further practical level, you cannot advertise what you do not demonstrate, and a failure to use actual end points will limit your subsequent marketing claims.

For a blood-pressure lowering agent such as metoprolol, the primary end point is diastolic blood pressure. For an anti-inflammatory such as Motrin, it might be either the duration or the extent of the inflammation. For a coronary-stenosis reducing surgical procedure or device, it might be the percentage of stenosis or the percentage of the population with less than 50% stenosis (termed "binary restenosis").

An exact quantitative definition should be provided for each end point. You also will need to specify how the determination will be made and who will make it. Subjective? Objective? By the treating physician? Or by an independent testing laboratory? Is the baseline measurement to be made before or after surgery?

In a study of several devices for maintaining flow through coronary arteries, the surgeon who performed the operation made the initial determination of stenosis. But it was decided that the more accurate

and "official" reading would be made from an angiogram by an independent laboratory.

How much give in dates is permitted?—patients have been known not to appear as scheduled for follow-up exams. What if a patient dies during the study or requires a further remedial operation? How is the end point of such a patient to be defined?

Don't put these decisions off till some later date; make them now and make them in writing lest you risk not collecting the data you will ultimately need.

Secondary End Points

Secondary[11] end points are used most often to appraise the *safety* of an intervention.

For a blood-pressure lowering agent like metoprolol these might include dizziness and diarrhea. But the systolic blood pressure would also be of interest.

For an anti-inflammatory, the most important are intestinal bleeding and ulcers. How does one detect and measure intestinal bleeding? Two ways, by self-evaluation and by measuring the amount of blood in the stool. Data relating to both must be collected.

For a coronary-stenosis reducing surgical procedure or device, the primary concern is with other procedure- and condition-related adverse events including death, myocardial infarctions, and restenosis severe enough to require further operations.

To ensure that you will collect all the data you need, a careful review of past clinical and pre-clinical experience with the present and related interventions is essential. For example, suppose that extremely high doses of your new agent had resulted in the presence of abnormal blood cells in mice. While such abnormal cells may be unlikely at the therapeutic dose you are using in the trials, to be on the safe side, blood tests should be incorporated in the trial's follow-up procedure.

Don't Collect Data You Don't Need

Store and Analyze the Data You Do Collect

During the trial and afterward, you will probably want to record the frequency of all adverse events, of specific adverse events, and of

[11]The use of the terms "primary" and "secondary" can be misleading. Quite often in long-term clinical trials we are already confident in the efficacy of a treatment but are extending the duration of the trial so that we can be equally certain of the absence of long-term negative effects.

CHECKLIST OF MEASUREMENTS	
What is the nature of your intervention?	What quantitative results do you expect?
How will it be administered?	You must test for safety.
What is its duration?	What short-term side effects are expected?
You are planning to test for efficacy.	How do you plan to measure them?
What are your primary end points?	What quantitative results do you expect?
When will the measurements be made?	How soon can you expect to observe them?
How will the measurements be made?	What long-term side effects are expected?
Who will make them?	How do you plan to measure them?
What units will be used?	What quantitative results do you expect per 100 patients?
Who will interpret the measurements?	

those events directly related to the intervention that exceed a certain level of severity.

You should also determine *how* the adverse event data are to be collected. By use of a checklist—"Since your last appointment, did you experience fever? nausea? dizziness?" Or a volunteered response—"Have you had any problems since your last visit?" Elicited responses tend to yield a higher frequency of complaints. To be on the safe side, use both methods. Of course, hospitalizations, emergency treatment, and phoned-in complaints between visits must always be recorded.

Some secondary end points may also concern efficacy. For example, in a study of sedatives, you might be interested in how rapidly the patient obtained relief.

Tertiary End Points. Tertiary end points such as costs may or may not be essential to your study. Don't collect data you don't need. When in doubt, let your marketing department be your guide.

BASELINE DATA

You will need to specify what baseline data should be gathered prior to the start of intervention and how it will be gathered—by interview, questionnaire, physical examination, specialized examinations (angiograms, ultrasound, MRI), and/or laboratory tests. Baseline data

will be used both to determine eligibility and, as discussed in the next chapter, to stratify the patients into more homogeneous subgroups.

Be comprehensive. Unexpected differences in outcome (or lack thereof) may be the result of differences in baseline variables. What isn't measured can't be accounted for.

WHO WILL COLLECT THE DATA?

One further step involves grouping the questions in accordance with the individual who will be entering the data, for example, demographics and risk factors by the interview nurse with review by the physician, and laboratory results by the lab itself or by the individual who receives the report. These groupings will form the basis for programming the case report forms (see Chapter 10).

Finally, I would recommend you charge specific individuals with the responsibility of addressing each of the points raised in the preceding sections. The design committee can then function as a committee should in reviewing work that has already been performed.

QUALITY CONTROL

The secret of successful clinical trials lies in maintaining the quality of the data you collect. The most frequent sources of error are the following:

- **Protocol deviations that result when the intervention is not performed/administered as specified**
- **Noncompliance of patients with the treatment regimen**
- **Improperly labeled formulations**
- **Improperly made observations**
  - **Inaccurate measuring devices**
  - **Inconsistent methods of observation, the result of**
    - **Ambiguous directions**
    - **Site-to-site variation**
    - **Time-period to time-period variation**
  - **Fraud (sometimes laziness, sometimes a misguided desire to please)**
- **Improperly entered data**
- **Improperly stored data**

Among the more obvious preventive measures are the following:

1. **Keep the intervention simple. I am currently serving as a statistician on a set of trials where, over my loudest protests, each**

patient will receive injections for three days, self-administer a drug for six months, and attend first semiweekly and then weekly counseling sessions over the same period. How likely are these patients to comply?

2. **Keep the experimental design simple (see Chapter 6).**
3. **Keep the data collected to a minimum.**
4. **Pretest all questionnaires to detect ambiguities.**
5. **Use computer-assisted data entry to catch and correct data entry errors as they are made (see Chapter 10).**
6. **Ensure the integrity and security of the stored data (see Chapter 11).**
7. **Prepare a highly detailed procedures manual for the investigators and investigational laboratories to ensure uniformity in treatment and in measurement. Provide a training program for the investigators with the same end in mind.**

   This manual should include precise written instructions for measuring each primary and secondary end point. It should also specify *how* the data are to be collected. For example, are data on current symptoms to be recorded by a member of the investigator's staff, or by the self-administering patient?
8. **Monitor the data and the data collection process. Perform frequent on-site audits. In one series of exceptionally poorly done studies Weiss et al. (2000) uncovered the following flaws:**
   - **Disparity between the reviewed records and the data presented at two international meetings**
   - **No signed informed consent**
   - **No record of approval for the investigational therapy**
   - **Control regimen not as described in the protocol**
9. **Inspect the site where the drugs or devices are packaged; specify the allowable tolerances; repackage or relabel drugs at the pharmacy so that both the patient's name and the code number appear on the label; draw random samples from the delivered formulations and have these samples tested for potency at intervals by an independent laboratory.**
10. **Write and rewrite a patient manual to be given to each patient by their physician. Encourage and pay investigators to spend quality time with each patient. Other measures for reducing dropouts and ensuring patient compliance are discussed in Chapter 9.**

STUDY POPULATION

Your next immediate question is how broad a patent to claim. That is, for what group of patients and for what disease conditions do you feel your intervention is appropriate?

Too narrow a claim may force you to undertake a set of near duplicate trials at a later date. Too broad a claim may result in

withdrawal of the petition for regulatory approval simply because the treatment/device is inappropriate for one or more of the subgroups in the study (e.g., infants and pregnant women). This decision must be made at the design stage.

Be sure to have in hand a list of potential contra-indictions based on the drug's mechanism of action as well as a list of common medications with which yours might interact. For example, many lipid-lowering therapies are known to act via the liver, and individuals with active liver disease are specifically excluded from using them. Individuals using erythromycin or oral contraceptives might also have problems. If uncertain about your own procedure, check the package inserts of related therapies.

Eligibility requirements should be as loose as possible to ensure that an adequate number of individuals will be available during the proposed study period. Nonetheless, your requirements should exclude all individuals

- **Who might be harmed by the drug/device**
- **Who are not likely to comply with the protocol**
- **For whom the risks outweigh any possible benefits**

Obviously there are other protocol-specific criteria such as concurrent medication that might call for exclusion of a specific patient.

Generally, the process of establishing eligibility requirements like that of establishing the breadth of the claim is one of give and take. The emphasis of the "give" being to recruit as many patients as possible, the "take" being based on the recognition that there is little point in recruiting patients into a study who are unlikely to make a positive contribution to the end result.

As well as making recruitment difficult—in many cases a pool of 100 potential subjects may yield only 2 or 3 qualified participants—long lists of exclusions also reduce the possibility of examining treatment responses for heterogeneity, a fact that raises the issue of generalization of results (e.g., see Keith, 2001).

In limiting your claims, be precise. For example, "exclude all those with diastolic blood pressure over

BEGIN WITH YOUR REPORTS

Imagine you are doing a trial of cardiac interventions. A small proportion of patients have more than one diseased vessel. Would you:

- Report the results for each vessel separately?
- Report the results on a patient-by-patient basis, choosing one vessel as representative? using the average of the results for the individual vessels?
- Restrict the study to patients with only a single diseased epicardial vessel?

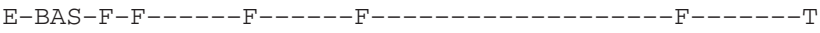

FIGURE 5.1 Trial Time Line Example. (E) Eligibility determination and initial baseline measurements; (B) baseline measurements; (A) assignment to treatment; (S) start of intervention; (F) follow-up exam; (T) final follow-up exam and termination of trial. Time scale in weeks.

105 mm Hg as measured on two occasions at least one week apart." A less precise statement, such as "exclude those with severe hypertension" is not adequate and would be a future source of confusion.

Though your ultimate decision must, of necessity, be somewhat arbitrary, remember that a study may always be viewed as one of a series. Though it may not be possible to reach a final conclusion (at least one acceptable to the regulatory agency) until all the data are in, there may be sufficient evidence at an earlier stage to launch a second broader set of trials before the first set has ended.

TIMING

Your next step is to prepare a time line for your trials as shown in Figure 5.1, noting the intervals between the following events:

- **Determination of eligibility**
- **Baseline measurement**
- **Treatment assignment**
- **Beginning of intervention**
- **(If applicable) Release from hospital**
- **First and subsequent follow-ups**
- **Termination.**

Baseline observations that could be used to stratify the patient population should be taken at the time of the initial eligibility exam. (See the next chapter for a more complete explanation.) The balance of the baseline measurements should be delayed until just before the beginning of intervention, lest there be a change in patients' behavior. Such changes are not uncommon, as patients, beginning to think of themselves as part of a study, tend to become more health conscious.

Follow-up examinations need to be scheduled on a sufficiently regular basis that you can forestall dropouts and noncompliance, but not so frequently that study subjects (on whose shoulders the success of your study depends) will be annoyed.

CLOSURE

You also need to decide now and document how you plan to bring closure to the trials. Will you follow each participant for a fixed period? Or will you terminate the follow-up of all participants on a single fixed date? What if midway through the trials, you realize your drug/device poses an unexpected risk to the patient? Or (hopefully) that your drug/device offers such advantages over the standard treatment that it would be unethical to continue to deny control patients the same advantages. We consider planned and unplanned closure in what follows.

Planned Closure

Enrollment can stretch out over a period of several months to several years. If each participant in a clinical trial is followed for a fixed period, the closeout phase will be a lengthy one, also. You'll run the risk that patients who are still in the study will break the treatment code. You'll be paying the fixed costs of extended monitoring even though there are fewer and fewer patients to justify the expenditure.

TABLE 5.1 Comparison of Closeout Policies

	Enrollment Phase	Closeout	Total
Fixed term	9 months	12 months	21 months
Fixed date	9 months	12 to 21 months	21 months

WHO WILL DO THE MONITORING?

Monitoring for quality control purposes will be performed by a member of your staff, as will monitoring for an unusual frequency of adverse events. But at certain intermediate points in the study, you may wish to crack the treatment code to see if the study is progressing as you hoped. Cracking the code may also be mandated if there have been an unusual number of adverse events. If a member of your staff is to crack the code, she should be isolated from the investigators in order not to influence them with the findings. The CRM should not be permitted to crack the code for this very reason.

One possibility is to have an independent panel make the initial and only review of the decoded data while the trials are in progress. Greenberg Report (1988) and Fleming and DeMets (1993) have offered strong arguments for this approach, while Harrington et al. (1994) have provided equally strong arguments against.

Our own view is that a member of your staff should perform the initial monitoring but that modification or termination of the trials should not take place until an independent panel has reviewed the findings. (Panel members would include experts in the field of investigation and a statistician.)

And you'll still be obligated to track down each patient once all the data are in and analyzed in order for their physicians to give them a final briefing.

By having all trials terminate on a fixed date, you eliminate these disadvantages while gaining additional, if limited, information on long-term effects. The fixed date method is to be preferred in cases when the study requires a large number of treatment sites.

Unplanned Closure

A major advantage of computer-assisted direct data entry is that it facilitates monitoring the results to obtain early indications of the success or failure of the drug or device that is under test. (See Chapter 14.) Tumors regress, Alzheimer's patients become and stay coherent, and six recipients of your new analgesic get severe stomach cramps. You crack the treatment code and determine that the results favor one treatment over the other. Or, perhaps, that there is so little

BEWARE OF HOLES IN THE INSTRUCTIONS

The instructions for Bumbling Pharmaceutical's latest set of trials seemed almost letter perfect. At least they were lengthy and complicated enough that they intimidated anyone who took the time to read them. Consider the following, for example:

"All patients will have follow-up angiography at eight ±0.5 months after their index procedure. Any symptomatic patient will have follow-up angiograms any time it is clinically indicated. In the event that repeat angiography demonstrates restenosis in association with objective evidence of recurrent ischemia between zero and six months, that angiogram will be analyzed as the follow-up angiogram. An angiogram performed for any reason that doesn't show restenosis will qualify as a follow-up angiogram only if it is performed at least four months after the index intervention.

"In some cases, recurrent ischemia may develop within 14 days after the procedure. If angiography demonstrates a significant residual stenosis (>50%) and if further intervention is performed, the patient will still be included in the follow-up analyses that measure restenosis."

Now, that's comprehensive. Isn't it? Just a couple of questions: If a patient doesn't show up for their eight-month follow-up exam, but does appear at six months and one-year, which angiogram should be used for the official reading? If a patient develops recurrent ischemia 14 days after the procedure and a further intervention is performed, do we reset the clock to zero days?

Alas, these holes in the protocol were discovered by Bumbling's staff only *after* the data were in hand and they were midway through the final statistical analysis. Have someone who thinks like a programmer (or, better still, have a computer) review the protocol before it is finalized.

difference between treatments as to fail to justify continuing the trials.[12] You have the findings confirmed by your external review panel (see sidebar). Do you and should you discontinue the trials?

One school of thought favors that you continue the trials but modify your method of allocation to treatment. If the early results suggest your treatment is far the superior, then two-thirds or even three-fourths of the patients admitted subsequently would receive your treatment, with a reduced number continuing to serve as controls (e.g., see Wei et al., 1990). Others would argue that continuing to deny the most effective treatment to *any* patient is unethical. The important thing is that you decide in advance of the trials the procedures you will follow should a situation like this arise.

If you find it is your product that appears to be causing the stomach cramps, you'll want a thorough workup on each of the complaining patients. It might be the cramps are the result of a concurrent medication; clearly, modifications to the protocol are in order. You would discontinue giving the trial medication to patients taking the concurrent medication but continue giving it to all others. You'd make the same sort of modification if you found that the negative results occurred only in women or in those living at high altitudes.

My advice. Set up an external review panel that can provide unbiased judgments.

BE DEFENSIVE. REVIEW. REWRITE. REVIEW AGAIN

The final step in the design process is to review your proposal with a critical eye. The object is to anticipate and, if possible, ward off external criticism. Members of your committee, worn out by the series of lengthy planning meetings, are usually all too willing to agree. It may be best to employ one or more reviewers who are not part of the study team. (See Chapter 8.)

Begin by reducing the protocol to written form so that gaps and errors may be readily identified. You'll need a written proposal to submit to the regulatory agency. And, as personnel come and go throughout the lengthy trial process, your written proposal may prove the sole uniting factor.

Lack of clarity in the protocol is one of the most frequent objections raised by review committees. Favalli et al. (2000) reviewed several dozen protocols looking for sources of inaccuracy. Problems in data management and a lack of clarity of the protocol and/or case

[12]See Greene et al. (1992) for other possible decisions.

report forms were the primary offenders. They pointed out that training and supervision of data managers, precision in writing protocols, standardization of the data entry process, and the use of a checklist for therapy data and treatment toxicities would have avoided many of these errors.

Reviewing the university group diabetes program study, Feinstein (1971) found at least five significant limitations:

1. **Failure to define critical terms, such as "congestive heart failure." Are all the critical terms in your protocol defined? Or is there merely a mutual unvoiced and readily forgotten agreement as to their meaning? Leaving ambiguities to be resolved later runs the risk that you will choose to resolve the ambiguity one way and the regulatory agency another.**
2. **Vague selection criteria. Again, vagueness and ambiguity only create a basis for future disputes.**
3. **Failure to obtain important baseline data. You and your staff probably have exhausted your own resources in developing the initial list so that further brainstorming is unlikely to be productive. A search of the clinical literature is highly recommended and should be completed before you hire an additional consultant to review your proposal.**
4. **Failure to obtain quality-of-life data during trial. Your marketing department might have practical suggestions.**
5. **Failed to standardize the protocol among sites. Here is another reason for developing a detailed procedures manual. Begin now by documenting the efforts you will make through training and monitoring to ensure protocol adherence at each site.**

Other frequently observed blunders include absence of concealment of allocation in so-called blind trials, lack of justification for nonblind trials, not using a treatment for the patients in the control group, inadequate information on statistical methods, not including sample size estimation, not establishing the rules to stop the trial beforehand, and omitting the presentation of a baseline comparison of groups. These topics are covered in the next chapter.

CHECKLIST FOR DESIGN

Stage I of the design phase is completed when you've established the following:

- **Objectives of the study**
- **Scope of the study**
- **Eligibility criteria**
- **Primary and secondary endpoints**

- **Baseline data to be collected from each patient**
- **Follow-up data to be collected from each patient**
- **Who will collect each data item**
- **Time line for the trials**

Stage II of the design phase is completed when you've done the following:

- **Determined how each datum is to be measured**
- **Determined how each datum is to be recorded**
- **Grouped the data items that are to be collected by the same individual at the same time (see Chapter 10)**
- **Developed procedures for monitoring and maintaining the quality of the data**
- **Determined the necessary sample size and other aspects of the experimental design (see the next chapter)**
- **Specified how exceptions to the protocol will be handled (see Chapter 7)**

BUDGETS AND EXPENDITURES

> **"Those who will not learn from the lessons of history will be forced to repeat them."**

Begin now to track your expenditures. Assign a number to the project and have each individual who contributes to the design phase record the number of hours spent on it. See Chapter 15.

FOR FURTHER INFORMATION

A great many texts and journal articles offer advice on the design and analysis of clinical trials. We group them here into three categories:

1. **General-purpose texts**
2. **Texts that focus on the conduct of trials in specific medical areas**
3. **Journal articles**

General-Purpose Texts

Chow S-C; Liu J-P. (1998). *Design and Analysis of Clinical Trials: Concept and Methodologies*. New York: Wiley.

Cocchetto DM; Nardi RV. (1992). *Managing the Clinical Drug Development Process*. New York: Dekker.

Friedman LM; Furberg CD; DeMets DL. (1996). *Fundamentals of Clinical Trials*, 3rd ed. St. Louis: Mosby.

Iber FL; Riley WA; Murray PJ. (1987). *Conducting Clinical Trials*. New York: Plenum Medical.

Mulay M. (2001). *A Step-by-Step Guide to Clinical Trials.* Sudbury, MA: Jones and Bartlett.

Spilker B. (1991). *Guide to Clinical Trials*. New York: Raven Press.

Texts Focusing on Specific Clinical Areas

Goldman DP, et al. (2000). *The Cost of Cancer Treatment Study's Design and Methods.* Santa Monica, CA: Rand.

Kertes PJ; Conway MD, eds. (1998). *Clinical Trials in Ophthalmology: A Summary and Practice Guide.* Baltimore: Williams and Wilkins.

Kloner RA; Birnbaum Y; eds. (1996). *Cardiovascular Trials Review.* Greenwich, CT: Le Jacq Communications.

Max MB; Portenoy RK; Laska EM. (1991). *The Design of Analgesic Clinical Trials*. New York: Raven Press.

National Cancer Institute. (1999). *Clinical Trials: A Blueprint for the Future*. Bethesda, MD: National Institutes of Health.

Paoletti LC; McInnes PM, eds. (1999). *Vaccines, From Concept to Clinic: A Guide to the Development and Clinical Testing of Vaccines for Human Use*. Boca Raton, FL: CRC Press.

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Online Guidelines

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