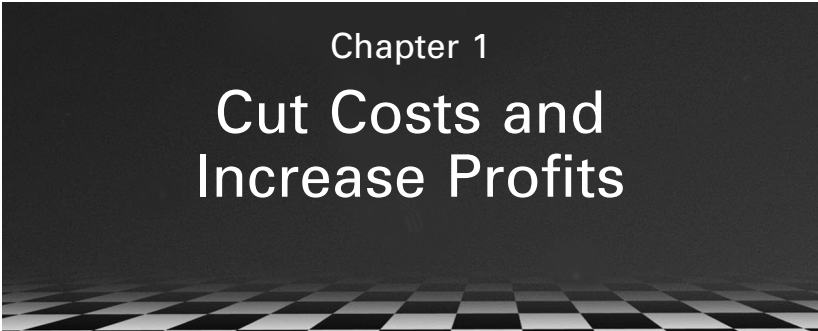


Chapter 1

Cut Costs and Increase Profits



THE ESSENCE OF THE GUIDELINES presented here—start with your reports, enter the data directly into the computer, validate on entry, and monitor your results continuously—first appeared in a newsletter I edited in the mid-1980s. The reactions of readers then ranged from tepid to outwardly hostile: “We can’t afford to give every physician a computer,” raged one data manager, ignoring the \$10,000 per patient that is the normal minimal expense for clinical data. “What will become of all the people we’ve trained as encoders?” moaned another months before the furious downsizing that characterized the late ’80s.

Such reactions make even less sense today when desktop computers are available for less than \$1000 apiece (and are even lower priced when purchased 25 or 100 at a time), every corporation is leaner and meaner than it has ever been, and regulatory agencies around the globe actively solicit electronic submissions. Yet everywhere we look the same old-fashioned, outmoded, and hopelessly inefficient procedures are still in place.

NO EXCUSE FOR THE WASTAGE

There is no excuse for the wastage and only one explanation: Middle management in pharmaceutical and device companies have focused on their own survival, not the corporation’s. They have minimized risks by doing what was done before and in consequence have placed the company at risk. They have developed elaborate time-consuming schemes to make today’s paperless system function as though we still

A Manager’s Guide to the Design and Conduct of Clinical Trials, by Phillip I. Good
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had to carve out each letter by hand and cost their companies millions in unnecessary added costs and millions more in lost profits because of the delays.

And why the delays? So our manager won't rock the boat, be caught innovating, or, worse, bring on board persons with skills that fail to match existing job descriptions.

But the bottom line is that electronic data capture coupled with careful monitoring will cut costs and shorten the time to realizing profit.

FRONT-LOADED SOLUTION

This text is about a great deal more than computer-aided data entry. The essence of the solution is that we need to spend far more time on planning, less on the repairs.

My pessimism stems, in part, from my having spent the last twenty-five years as a consultant to drug and device firms. As a consultant, I was always called in at the last moment to "fix" the problem. The "fix" took months and was generally unsatisfactory, and all hope of profit vanished when the competitor was first to market.

I worked full time once, too, for a fast-track boss who'd earned his spurs as a firefighter. He put down every preventive measure I proposed. But then, what's a firefighter without a fire?

The solutions offered to you here are front-loaded and may seem expensive. But by putting in the preventive planning effort now, your company will avoid far more time-consuming and expensive delays later.

Anyone who has ever spent much time on the water (or in the air) knows that once underway it is far better to under- than to oversteer.

On the other hand, no experienced sailor (or aviator) would consider getting underway without first making sure all systems were fully functional and life jackets, life raft, and emergency rations ready if needed.

I can understand and occasionally sympathize when biotech start-ups attempt to cut corners by doing the absolute minimum until they (and, more important, their investors) can

TWO APPROACHES TO MANAGEMENT

1. Tentative but responsible, avoids precipitous action and waits to see how the situation will develop before intervening.
 2. Envisions the worst and plans for it.
- Effective managers employ both.

be confident the project will be successful. It ends up costing these companies and their investors more in the end—not infrequently, an entire set of trials must be repeated all over from the beginning—but if you don’t have money and must wait upon the necessary venture capital, what choice do you have?

The puzzle comes when a large well-capitalized firm makes the same errors, errors that can only be attributed to poor management and slothful minds that simply hope to defer the inevitable.

DOWNSIZING

Take downsizing as one example of sloppy management. Too often, downsizing has taken place by percentages and not in terms of the skills the modern corporation needs. Stand back, see what you are trying to accomplish, then hire, or, better still, retrain in accordance with current requirements.

Developing all the details of safety and efficacy assessment, data gathering, and recruitment before one begins demands time and patience. The counterargument that one cannot foresee every contingency is largely false. When one is forced to lay out all the elements of a design before commencing a study, one often manages to foresee 99.9% of the potential problems. Throwing up your hands and crying, “It’s just too difficult, let’s wait for the data,” is the act of a child, not of a mature manager.

Often, those in upper management cannot understand the delay. Yet the tale of the ever-befuddled Bumbling Pharmaceutical and Device Company told in the chapters that follow is too often the case in all too many clinical studies. The high price of pharmaceuticals today masks the costs of ineptitude.

THINK TRANSNATIONAL

Once optimal dose levels and procedures have been established through Phase I and Phase II trials, begin to think on a transnational basis. Most large-scale trials are multicenter trials. By establishing your trial centers in several different countries, you’ll have taken the first steps toward obtaining transnational approvals at no increase in costs.

The United States, Japan, and the European Union have already embraced the concept of the common technical document, simpli-

Electronic data capture cuts costs and shortens the time to realizing profit.

fyng the transnational submission process. The single set of standards makes it easier than ever to plan and coordinate your trials. And the transnational approach means an improved bottom line as your firm's new product reaches multiple markets simultaneously. It's good politics and can provide for more heterogeneous trial populations.

A FINAL WORD

For the vast majority of readers, no explanation of why we do clinical trials is necessary. Supervising or participating in clinical trials may even be your primary occupation. Still, there may be a few of you, inventors and entrepreneurs, who are asking just why your drug/device can't be marketed without expensive trials. It's been tested in the lab: You know it works.

The obvious reason is that the regulatory agency won't let you market your intervention without trials. But there is a greater, more important motivation:

Without an organized, well-controlled randomized clinical trial, a single run of bad luck, a whim of fate, could forever deny the public a promising cure and you and your company justified profits. Think of the controversy surrounding silicon implants. Women got sick, sued,

and won millions in damages without the slightest scientific evidence supporting their claims. Manufacturers went bankrupt; hundreds of women had (as it proved, unnecessary) surgery to remove the implants. Yet these bankruptcies could have been avoided had the manufacturers of that period sponsored a well-controlled clinical trial.¹

For your product to achieve the full success it deserves, you need to know what kind of individuals will respond best to the new treatment and what kind would do best to avoid it. Controlled large-scale clinical trials are the *only* way to get the answers you need.

IN THE NEWS

"German prosecutor launches probe against Bayer over how the company handled the withdrawal of Baycol/Lipobay, the anti-cholesterol drug that has been linked to fatal side effects." *Financial Times*, 4 September 2001. (In the litigious United States, just call 1-877-Toxic-RX to become part of a class action suit against Bayer.)

"Baxter recalls blood filters after deaths." *Financial Times*, 4 September 2001.

"Class action suit challenges Pfizer over the way it conducted clinical trials in Nigeria five years ago." *Financial Times*, 3 September 2001.

¹Angell M (1996) *Science on Trial: The Clash of Medical Evidence and the Law*, New York: Norton.

CLINICAL TRIALS

Clinical trials consist of a randomized comparison over a fixed period of time of an intervention method (drug, device, or biological alteration) of interest against an established standard or a negative control (placebo).

The trials are normally preceded by in numero (computer), in vitro (cell culture), and in vivo (animal) experiments, both acute (one time) and chronic (over an extended period), and, in some cases, retrospective studies of the effects of the intervention in humans.

The initial Phase I or *safety trials* focus on the potential adverse effects of the intervention in humans. In the case of drugs and biologics, these trials are used to establish maximum acceptable dose levels (and the minimum toxic dose). They generally involve only a small number of subjects and a one-time or short-term intervention. An extended period of several months may be used for follow-up purposes.

The subsequent Phase II or *efficacy trials* are used to establish minimum effective dose levels and to obtain some idea of the nature of secondary responses to the intervention and possible adverse side effects.

The focus of this text is the final or Phase III clinical trial. These involve large numbers of subjects (500 to 5000), studied over an extended period of time (2 to 5 years) with the possibility of an even longer ongoing follow-up. The larger number of subjects in this type of trial provides an opportunity to study the effects of the intervention on different subgroups (women as well as men, smokers as well as nonsmokers, diabetics and nondiabetics) and to assess the effects of concurrent medications and various risk factors on the ultimate outcome. The longer time period provides for an assessment of the effects of chronic usage along with any other long-term effects.

Aspirin is unparalleled for its ability to ease pain, reduce fever, and suppress inflammations. I carry a couple of aspirin with me in the car because I've read that taking an aspirin during or just after a heart attack could save my life. But if I were already taking an anticoagulant, an aspirin could mean death.

On the back of the aspirin bottle, in large bold print, much larger than the other writing you'll find on the label, are the words, "It is especially important not to use aspirin during the last three months of pregnancy unless specifically directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery." Important words that when written in the language of the potential consumer will forestall lawsuits.²

In what follows, we provide guidelines for your trials and a prescription for success. We tell you the contingencies you need to plan

²Ramirez v. Plough, Inc., 6 Cal.4th 539.

for and the design decisions you need to make. We show you how to conduct and monitor long-term clinical trials and, finally, how to review the results so you can be still more effective in the trials of your next successful product.

Every profession likes to cloak its actions, even the simplest, in arcane language virtually unintelligible to outsiders (statisticians and computer scientists are particular offenders). We've tried our best to describe the work of the innumerable specialists in terms all can understand. Although I have many scholarly publications, my articles also have appeared in airline magazines, *Sports Now*, *Volleyball Monthly*, and a half-dozen newspapers. Hopefully, you'll understand everything I've written, the first time through.

I'd recommend you read this book twice, though: The first time to get an overview, and the second (and, perhaps, the third) time on a chapter-by-chapter basis as each stage in your trials arises. Each chapter contains checklists, so you might want to retain a copy of this book for yourself and put a second copy in the hands of the specialist who will be carrying out that chapter's functions.

Specialists (even statisticians and computer programmers) will also find this text of interest, not only for the checklists and lists of further readings that come with each chapter, but because this book covers and, hopefully, clarifies the activities of all the other members of the project team.

Thanks for reading.

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