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Introduction to Clinical Trials

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1.1 GOALS OF CHAPTER

The purpose of this chapter is to consider the overall goals and requirements of conducting clinical trials. It is an opportunity to avoid pitfalls by viewing the larger picture. This chapter seeks to provoke consideration of key issues without duplicating the more detailed work of later chapters.

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1.2 GOALS OF CLINICAL TRIALS AND WHAT IS AT STAKE

The ultimate goal of drug development is the creation of new, safe, and effective compounds for treating human disease. Clinical trials comprise the portion of this endeavor involving human subjects. While the basic tenants of scientific inquiry do not differ from preclinical research, the stakes are higher and the regulations more stringent.

The cost of conducting clinical trials can be measured in two ways: the human cost and the resource cost. The human cost is the cost from the patient's perspective. The patient suffers from a condition dire enough that experimental therapy is a consideration. He or she holds out hope for this therapy and trusts to the scientific skill and integrity of those conducting the trial. The patients expose themselves to an incompletely understood therapy and usually suffer some degree of toxicity in order to gain uncertain benefit. Prior to a drug being declared useful or not, hundreds or thousands of patients may be involved in trials related to the drug.

On another balance sheet, there is the impressive economic burden of drug development. The cost of successfully bringing a new drug to market is now in the range of $800 million [1]. The interval between the start of clinical testing and the submission of an application for regulatory approval of a new drug is estimated at 6 years [1]. Even so, fields such as oncology are seeing an increase in drugs under study [2]. Yet there are limits to the number of clinical centers able to conduct trials. More importantly, there is a limit to the number of patients that are eligible to participate in a given trial, either by reason of demographic factors, comorbidity, incompatible disease parameters, or willingness. These limitations suggest that investigators must be selective about which drugs they study in clinical trials.

While drug discovery still involves an element of happenstance, contemporary drug development is ever more focused on mechanisms specific to a given disease. Frequently, therefore, a disease population will have been targeted during preclinical development. It is up to the clinical trials process to assess whether the new agent is both safe and effective in this or other populations. Generally, the first concern is assessing drug toxicity and the related dosing and pharmacokinetics. Following this, some evidence of efficacy is sought. If it is found, efficacy must be confirmed in larger, randomized trials. Finally, postmarketing surveillance studies may be performed. These successive clinical trials are usually categorized by phase, and these phases will be introduced below.

1.3 INTRODUCTION TO PHASE I–IV CLINICAL TRIALS

1.3.1 Introduction to Phase I Trials

Purpose New drugs are first introduced into human subjects in phase I trials. The primary goal of these first studies is to assess the safety of the agent and to determine an acceptable dose for further study. Related goals include the assessment of pharmacokinetics as well as pharmacodynamics. To study pharmacokinetics is to study how the body affects the drug: How is the drug absorbed? How is the drug distributed between body compartments? How is the drug metabolized and excreted? Pharmacodynamics is the relationship between drug exposure and drug effect. Here

we ask what normal physiological or disease processes are altered when a drug is administered at varying doses.

Methods The method used is to some extent dictated by the drug and disease under consideration. In fields other than oncology, phase I trials are typically undertaken in healthy volunteers. Typically, increasing doses of a drug are employed in small successive cohorts of patients. Each cohort is assessed, and subsequent dose levels are only used if excessive toxicity (often termed dose-limiting toxicity) is not encountered. At each dose level, blood or other body fluid is taken for pharmacokinetic studies.

In oncology studies, the first and lowest dose level may be based upon animal toxicities (e.g., 10% of the dose that is lethal in 10% of mice (LD_{10})) and dose increments are often based upon a modified Fibonacci sequence (1, 2, 3, 5, 8, 13, ...), a scheme that decreases the dose increment with each subsequent level. The notion is to limit patient exposure to dose-limiting toxicity through more cautious later stage dose increases. Alternative dosing schemes employ one patient per dose level or a continuously modified dosing increment based upon observed toxicities; the goal of such alternative methods is to increase phase I efficiency and limit the number of patients who receive too little or too much drug [3]. At some point, toxicity is deemed to be excessive, and the appropriate dose level is then established, typically at the dose just below this point of excessive toxicity.

Pharmacokinetics is the study of the drug absorption, transport, distribution, metabolism, and elimination; the goal is to improve drug delivery and efficacy. An understanding of the molecular target may have implications for drug exposure. For example, antimetabolites used against cancer are considered to be most effective in the DNA (deoxyribonucleic acid) synthesis phase (S-phase) of the cell cycle. To best inhibit tumor growth, it is considered optimal to maintain a constant or prolonged exposure of the cancer to drug such that most cells are caught as they transit through S-phase. Pharmacokinetic analysis can tell the investigator if such an exposure is occurring and may prompt alternative dose schedules in subsequent studies.

Pharmacodynamic assays—assays that assess the effect of the drug on normal physiology or disease—may be useful in assessing whether a drug is likely to have a clinical effect. In cardiology, for example, the effects of a new agent on subjects' blood pressure or electrocardiogram may be relevant [4]. In studies of new antibodies or other targeted therapies, a therapeutic effect may be seen without the dose-dependent toxicities expected with other agents (e.g., the antimetabolite methotrexate used in rheumatoid arthritis or cancer). Conducting assays that demonstrate molecular changes in the relevant target could serve as a proof of concept for the agent; this, in turn, could prevent the need for higher dose levels, levels that could induce toxicity and would increase the duration of the study.

Results At the end of a phase I study, acute toxicities should be understood. Toxicities related to more long-term exposure may not be apparent until future studies are undertaken. In conjunction with the pharmacokinetic assays and any pharmacodynamic work, an assessment must be made as to whether further studies should be conducted, and, if so, at what dose. Pharmacokinetic analysis may suggest that changes in dose or dosing frequency are required. In instances where toxicity may be excessive at doses not expected or observed to have a useful biological

effect, further phase I studies may be designed to circumvent the toxicity. While preliminary activity against disease may be observed in phase I studies, the initial assessment of positive clinical outcomes is primarily the arena of phase II studies.

1.3.2 Introduction to Phase II Trials

Purpose Phase II studies are conducted to assess the initial activity of an agent against disease. Further information is gathered about an agent's adverse effects, and additional pharmacokinetic or pharmacodynamic studies may be conducted.

Methods Unlike phase I studies, which may employ many different doses of an agent, phase II trials typically employ one or occasionally a few dose levels. Larger cohorts of patients are exposed to the drug in order to observe one or more clinical endpoints. The measured endpoints will vary depending upon the drug and field of study. In trials of heart failure, for example, physiological parameters (e.g., ventricular remodeling) may be assessed in addition to clinical measures such as exercise tolerance [5, 6]. Vaccine studies typically assess safety and immune responses and may involve both treatment and control groups [7]. In oncology, tumor response (shrinkage) rates have traditionally been used as a measure of response, but newer targeted drugs have led to greater reliance upon endpoints such as stable disease rates. Prior to conducting the study, investigators should specify what minimal level of drug activity will be accepted as evidence to warrant subsequent investigation. Phase II studies should be designed as precursors to phase III studies.

Phase II studies may be single-arm assessments of drug activity; such studies have an implied comparator of prior trials or clinical experience. Alternatively, randomized studies may be conducted, comparing the experimental arm with either a placebo, a standard therapy control arm, another experimental arm, or different doses of the experimental arm itself. The randomized study, while of limited power, may improve drug development by increasing the likelihood of selecting the best drug or dose for further development [8]. When a standard treatment arm is used as a comparator, that arm may serve as a barometer for the severity or nature of the disease in the overall study cohort. Excellent or poor results in the experimental arm are interpreted in light of the control arm.

A more recent study type, the randomized discontinuation study, begins with a lead-in period in which all subjects receive the experimental arm. After a predetermined period, subjects are randomized between continuing the study drug and receiving a placebo or no therapy. The lead-in period eliminates noncompliant subjects and unresponsive disease, increasing the likelihood of differences being observed in the randomized portion of the study. The cost is in the greater number of patients required for the study due to drop-out in the initial nonrandomized period [9].

Results As noted, the clinical endpoints vary widely based upon disease and agent type. If a drug effect was seen, it must be considered whether the effect was sufficiently interesting in light of existing therapies or other study arms. If a clinical effect was not seen, one must assess whether this could be explained by any biological surrogates or pharmacokinetic studies also undertaken. The clinical efficacy must

be assessed in the face of observed toxicities. More severe toxicities might be acceptable for lifesaving therapies but not for agents directed at minor ailments. At the end of the phase II study, the investigator should have an initial assessment of a new agent's impact on a disease as well as a better understanding of the toxicity profile.

Two important and frequently used statistical concepts should be introduced here. The first is power. In clinical terms, power is the probability that a study will find that a drug is effective when the drug truly *is* effective. Statistically, it may be described as Power = $1 - \beta$, where β is the probability of a study finding a drug ineffective despite the truth being that the drug *is* effective—β is therefore also called the β error. A related term, the α error, represents the opposite mistake; it is the chance that a study will find a drug effective when in truth the drug is ineffective. By general agreement, the value of α is usually set at 0.05. Power increases with larger studies (i.e., more patients) and when more prespecified clinical events occur. Phases I and II trials typically employ small numbers of patients, which tends to increase error rates and limit statistical options. Nevertheless, statistics can inform us of the limitations of our knowledge. For example, if we observed 3 of 25 patients with cancer to have tumor responses, we could determine that—with 95% likelihood—the true response rate was from about 3–30% [10]. If we had hoped for better, we would need to carefully consider any next trial. Phases III and IV studies, described below, rely heavily on thoughtful consideration of α and β errors.

1.3.3 Introduction to Phase III Trials

Purpose Phase III studies are typically large randomized studies designed to demonstrate useful clinical activity in a specific disease setting. The process of randomizing patients between different treatment arms is fundamental to avoiding biased interpretations of outcomes.

Methods The design of phase III studies is critical both in addressing a specific hypothesis and in the pragmatic sense of making a drug useful in clinical practice. Fundamentally, this means that an appropriate patient population must be selected, all treatments must be clinically relevant, and the expected improvement in outcome must be both clinically meaningful and statistically measurable. Eligibility criteria—those criteria that determine which patients may join the study—must define a population that is both adequately generalizable to include patients representative of the diseased cohort but also homogeneous enough to retain statistical power and to be applicable to a usefully recognizable disease group. For example, studies may be difficult to interpret when they include both early- and late-stage patients. If a study is positive, to which population is it best applied? If negative, might it be positive in one of the disease subpopulations if a study were done only in that group.

Treatment arms cannot ignore previously existing therapies. With respect to heart failure, a new drug must take into account that many patients will also be on ACE (angiotensin-converting enzyme) inhibiters, β-blockers, diuretics, antiplatelet agents, and possibly other medications. Excluding these medications may make the study uninterpretable in the real-world clinical context and, more importantly, it may be unethical.

The endpoint of a phase III study should be an accepted and clinically relevant one that is specified before the trial is conducted. For example, in many cancers, an improvement in response rate is not considered an adequate phase III endpoint, whereas improvements in survival or disease-free survival may be accepted. Secondary endpoints—quality of life, for example—may be employed but must be recognized as such at study completion.

A common difficulty with phase III studies is inadequate power. This is often due to an overly optimistic estimate of improvement in a clinical outcome, an estimate that may be a product of resource limitations. A lesser and potentially meaningful improvement may be missed if too few patients are accrued to the study or follow-up is too short.

Results The primary and any secondary clinical outcomes must be assessed and interpreted as planned. In circumstances where the primary outcome is of borderline significance or where the primary and secondary clinical outcomes are disparate, explanations may be considered and used as hypotheses for future study. Post hoc analyses are frequently conducted but can only be hypothesis generating.

1.3.4 Introduction to Phase IV Trials

Purpose Phase IV studies, sometimes called pharmacoepidemiologic studies, are those that are conducted after a drug has been approved for marketing. Such studies, often large, may assess a drug for uncommon toxicities that may be undetectable in smaller phases I–III studies, or they may establish the activity or tolerability of a drug in a particular population or practice setting.

Studies conducted to assess new methods of drug administration, combinations with other agents, or activity in other diseases—that is, studies seeking a new marketing indication—are better described and conducted as the phases I–III studies they represent. Similarly, a distinction can be made between trials seeking to answer a specific postmarketing question and those conducted solely to increase market share, so-called seeding trials. In the latter, there may be an incentive for the involved physicians to prescribe the drug in question and there may be no intent to publish the results [11, 12].

Methods Phase IV studies may be conducted in several ways.

1. Descriptive studies, sometimes collections of drug toxicities captured over time, may identify new problems. These may range from case studies to series of patients collected by companies or regulatory bodies. Although resource intensive, large prospective cohort studies may also be conducted to capture infrequent adverse events.
2. Randomized studies may be used to compare an agent to other similar agents or to confirm earlier results.
3. Case–control studies or retrospective cohort studies can be conducted after data on a drug has accumulated. This would typically be done to assess for unusual side effects or associations of a drug with the development of a subsequent disease, such as malignancies or autoimmune sequelae.

4. Cross-sectional studies, although perhaps less useful, assess drug exposure and outcomes in a population at a specific time. Causality may be more difficult to assess if a sequential temporal relationship cannot be determined [12].

Results The results of phase IV studies may be required to fulfill regulatory requirements after accelerated approval of a new drug. The additional numbers and prolonged follow-up provided by postmarketing studies may also be crucial in revealing important but infrequent toxicities. On occasion, these findings may lead to the withdrawal of a drug from the market, as, for example, after cardiovascular complications were associated with the anti-inflammatory drug rofecoxib [13, 14].

1.4 PRINCIPLES OF TRIALS DEVELOPMENT

1.4.1 Big Picture, Small Picture

Overall Goal: Improved Patient Care The details involved in protocol design and regulatory requirements can be overwhelming. Remembering the fundamental goal of clinical research—improved patient care—can be an aid; study design and decision making should be influenced by the consideration of what is best for patients.

Patients seek relief from suffering. The investigator should therefore choose the most relevant endpoint for a given trial. Studies of rhinitis may reasonably examine patient reporting of nasal discharge and congestion [15], while studies of pancreatic cancer must consider an agent's impact on survival or more relevant measures of symptoms or quality of life. Research protocols must be designed with these parameters in mind. The outcome of interest must be described in sufficient detail that it may be easily replicated, a matter as important in assessing a study's value in support of regulatory approval as it is to an understanding of what benefit a drug may be to future patients. Any clinical trial must assess the toxicities associated with treatment. Known adverse effects must be clearly described and provisions made for the adjustment of treatment to mitigate such toxicities should they occur. Of course, for sufficiently severe toxicities, a warning system must be in place to inform patients, investigators, and the companies and agencies overseeing the study. The details of such reporting requirement may vary, but the act of sharing such information is sensible.

Quality After careful protocol development comes the messy process of administering a protocol. Invariably, aspects of the protocol appear to be open to interpretation, and at some point there will be lapses in study conduct or paperwork. The maintenance of quality in a study means always trying to adhere to the letter and spirit of the protocol. It means that the responsible investigator must be available to arbitrate whether patients are actually eligible and whether protocol violations have occurred. It means that study coordinators must vigorously pursue the complete assessment of patients and the related documentation. Every effort must be made to follow patients to the completion of study. A poorly followed or documented study may be difficult to interpret and may not be acceptable to regulatory agencies or other entities overseeing the trial.

Nothing in Isolation—The Bench and the Bedside The present era is one of exciting new agents, many directed at specific targets in the disease process. Even while such agents must undertake the staged clinical trials process, they may evoke interesting biological questions with implications for ongoing or future studies. The prospective collection, banking, and analysis of biological specimens may reveal subsets of patients for whom a new agent may have particular benefit.

For example, small-molecule tyrosine kinase inhibitors directed at the endothelial growth factor receptor (EGFR) have been investigated in patients with non–small cell lung cancer. Despite good preclinical data [16], clinical studies demonstrated more limited benefit, ultimately resulting in limitations of access to one such drug, gefitinib, previously approved by the Food and Drug Administration (FDA)under accelerated approval [17]. The investigation of tumor samples, however, revealed that some tumors had mutations in the tyrosine kinase domain of the *EGFR* gene, with corresponding protein changes and apparent improvements in clinical responses [18, 19]. Unfortunately, this finding was made posthumously for gefitinib, but the implications for future development of this class of drug are clear. When feasible, biological investigations and specimen preservation should continue during the clinical period of study.

1.4.2 Human Element

Differences between Mice and Humans Despite the fact that 99% of mouse genes have human counterparts [20], several important issues separate the species. First, important differences in biology can mean significantly different drug metabolism and elimination, such that pharmacokinetics can only be generally predicted [21]. Second, human xenografts planted in mice may respond to drug therapy, but such responses are not consistently predictive of response phase II clinical studies [22]. This supports the necessity of clinical studies. Third, ethics dictates that both the goals and conduct of preclinical and clinical studies must differ. In animals, while the suffering and distress of animals is to be minimized [23], it is accepted that toxicities must be observed in other species to understand new agents and protect the humans that are subsequently exposed. By contrast, the very structure of trials in humans is one of careful staging to avoid excessive toxicity or any death. Earlier studies establish safety while later studies assess for useful clinical activity of a drug.

Relevance of Ethics There are more and less obvious aspects of ethics involved in clinical drug development. We have fortunately recognized and codified the obvious, so, for example, it is universally recognized that withholding effective treatment for the sole purpose of observing natural disease history is unethical [24]. But there are less flagrant examples that affect study design.

The phase I study by its nature poses ethical conundrums. It is a study designed to assess toxicity and an acceptable dose for a drug, with clinical benefit being a secondary consideration. Thus, subjects put themselves at risk for uncertain benefit, and healthy volunteers stand no chance of clinical benefit. But the phase I trial is accepted for several reasons. First and foremost, if one accepts that our society wishes to continue to make progress against disease, it becomes an unavoidable necessity. A new drug must at some point be introduced into the human population.

This must be done in a careful and systematic fashion, but risk can only be minimized, not eliminated.

Second, patients who face the option of a phase I study are often those who have a disease without further standard therapeutic options. Although the chance of benefit for a given patient is likely to be very low, a chance for therapeutic success may be motivation enough [25], and altruism may play a smaller role in patient decision making than frequently thought [26]. Yet even when informed consent may be forthcoming, phase I studies are at greater risk than later phase studies for violating the principle of beneficence (i.e., offering insufficient benefit to justify risk) and for abusing the desperation of a vulnerable patient population at the expense of the ethical principle of justice [27].

Another challenging aspect of phase I studies is drug dosing. In oncology, it has been observed that benefit derived from new cytotoxic drugs occurs more frequently when doses are near the limit of acceptable toleration of side effects [28]. This means that patients who receive lower drug doses earlier in the study are less likely to have benefit, although they may also have less toxicity. Phase I dosing is therefore a balance between minimizing toxicity and maximizing any possible benefit for the greatest number of patients [25]. It is thus incumbent on investigators to carefully plan dosing increments during protocol development and assess side effects as the trial progresses.

Phase III studies, though more likely to confer benefit than phase I studies, still pose ethical challenges. One such difficulty is the decision about whether to stop a trial during interim analysis. A trial of hormone therapy (letrozole) after curative surgery for breast cancer was stopped at an interim analysis when the treated patients demonstrated lower rates of disease recurrence [29]. It may reasonably be asked whether such a study might better be continued blinded until longer follow-up was available or a survival difference was or was not found. While unquestionably it is better to avoid recurrence of breast cancer, the cost of adopting such therapy must be balanced against an incomplete study, other potentially better therapies, or trials that might be aborted by early adoption of the considered drug [30]. We are also accepting the financial cost of a new drug by its adoption. A society may reasonably consider for any therapy whether the gains so achieved are incurred at a reasonable cost in terms of other societal concerns. Such issues make it apparent that ethics is not a matter of nebulous constructs but an integral consideration for clinical trials.

Quality of Life Another aspect of research that separates the clinical from the preclinical phase is the human interpretation of ailments. From pain to dyspnea, humans demonstrate a range of subjective degrees of discomfort from the insults of disease [31, 32].

Although less concrete and more difficult to assess than endpoints such as survival or hospital admissions, quality of life or symptom control data can be meaningful to patients and clinicians. In circumstances where endpoints such as survival are not readily demonstrated, such as in rheumatoid arthritis, measurements of quality of life, symptoms, and function are useful to assess drug efficacy [33]. Investigators should endeavor to use validated scales so that the results are less open to question. Still, quality of life measures have provided challenges. How often does one conduct measurements? How does one account for the inevitably missing data points [34]?

In the field of oncology, quality of life scales alone have yet to prove sufficient for drug approval by the FDA. In contrast, other simple and easily comprehensible measures of pain or composite endpoints that include pain have been accepted as a basis for drug marketing [35].

1.4.3 Multidisciplinary Nature of Clinical Trials

Actors The manifold tasks and varied expertise required to conduct contemporary clinic trials necessitate the input and assistance of several groups. Prior to initiating a clinical trial, it must be assured that all the players are properly cued. Table 1 lists the persons and groups that typically must be available to conduct a trial, listed roughly in order of appearance but not importance.

Due to the diverse resources required to conduct clinical trials, it is not always practical for an organization to maintain capacity for every aspect of study conduct.

TABLE 1 Entities Involved in Clinical Trials

Entity	Role
Principle investigator	While not all trials are conceived by the principle investigator, the principle investigator is responsible for the overall conduct of the trial.
Funding agency/ company	This may be a corporate, government, or charitable agency. In addition to funding, companies may supply drug. These bodies are frequently involved in receiving and disseminating reports of adverse events.
Statistician	Statisticians are involved in study design, interim analyses, and the final analysis.
Study coordinators	Study coordinators are involved in all aspects of trials: protocol and form creation, submission of the protocol to various review boards and government regulatory agencies, patient consent and registration, as well as data collection, cleaning, and summation.
Contract and financial administrators	These persons negotiate agreements between funding agencies and centers conducting the trial, aid in the creation of budgets, and distribute funds necessary to conduct the trial.
Scientific review committee	This body reviews the scientific merit of a clinical trial and may suggest improvements.
Health/safety committee	Although not involved in all studies, this group is responsible for ensuring that investigators adhere to regulations regarding infectious and hazardous substances.
Institutional review board/ethics committee	This body assesses whether the study meets the standards of respect for persons, beneficence, and justice and will prohibit substandard studies.
Data safety monitoring board	Created before the initiation of the trial, this body provides objective oversight of the study and may recommend early closure of a study for reasons of either significant early benefit or excessive toxicity.
Pharmacists	Pharmacists are responsible for research drug control and accounting.
Nursing staff	Drug administration and sample collection requires both nursing staff and physical space, sometimes including facilities for overnight visits.
Pharmacokinetics specialists	Pharmacokineticists are usually involved in phase I drug design and sample collection and analysis but may also be involved in later phase studies.
Outcomes assessments staff (e.g., radiologists)	Depending upon the outcomes being assessed, radiologists or other specialists may be required to interpret study data. In some instances, independent and blinded individuals or groups may be used to assess study data in a more objective fashion.

For this reason, an industry of contract research organizations has arisen to provide research services not available from in-house sources. These organizations can provide services such as research ethics review, protocol preparation, study administration, regulatory consultation, and radiologic imaging support. They can offer the advantages of expertise and efficiency in trial conduct, with offsetting disadvantages of decreased control over details, the need to rely on the contract agency for quality, and the need for careful communication with respect to the hired agency's responsibilities and goals [36].

Statisticians The early inclusion of an experienced statistician is advisable for most studies. In order to obtain a useful study result, a hypothesis must be generated and a statistical test must be chosen prior to study conduct. *Post hoc* statistical analyses can lead to new hypotheses for future research but cannot generate definitive answers [37].

A statistician can help to clarify the question under consideration. For example, when conducting a phase II study in heart failure, one may wish to assess the difference in exercise duration between two treatment arms [6]. Using the expected or minimally acceptable difference and the desired error rates, a statistician can advise on the number of patients that need to be recruited to the trial. Failure to determine this need may result in a futile, underpowered study or one which unnecessarily exposes excess patients to an experimental therapy.

In larger, phase III studies, the patient exposure and resource stakes are typically greater. As with our phase II example, realistic expected differences between endpoints must be considered. It must be decided whether the new therapy is likely to be superior, or whether the investigator wishes only to demonstrate that it is noninferior (although either less toxic, more convenient, or substantially cheaper), as the sample size will be larger in the latter case and the hypothesis test different. The ethical challenges of the interim analyses were previously mentioned, but the statistical challenges can also be substantial. One must estimate how many events are required in a population to sufficiently conduct the analysis, then employ a test that will assess the difference while accounting for repeated statistical testing. The goal is to avoid both false-positive studies and prolongation of a futile trial [38].

Setting During study development, investigators must decide where the trial will be conducted: primarily among academic centers and cooperative organizations or in community centers, usually under the auspices of a pharmaceutical company and frequently organized by contract research organizations. In addition, a study will be domestic or international.

Traditionally, academic centers and organizations have conducted clinical trials, although this has been changing [39]. While the clinical trials infrastructure is more commonly in place in academic centers, community centers have demonstrated the ability to conduct clinical trials as effectively as academic centers [40–43], and organizations have formed that may efficiently recruit patients within such centers [39]. Community-center-based trials may have the advantage of a more generalizable patient population than that seen in academic centers [44, 45]. Limitations of community trials may include limited recruitment despite declared interest, a need for financial incentives, a need for easy documentation, and a lack

of perceived benefit to the physician [46] or managed care organization [47], although these characteristics are by no means exclusive to community trials [48]. The corporate control of data, use of for-hire ethics boards, and the greater dependence on financial incentives can leave some community trials more open to question [39]. Indeed, possibly as a result of publication bias and data control, publications of industry-sponsored work tend more often to report in favor of the experimental therapy [49]. For this reason, studies conducted by academic centers may offer superior credibility.

While the logistical and regulatory convenience of domestically conducted clinical trials is undisputed, there may be advantages to studies conducted on an international basis. Most evidently, the recruitment pool may be vastly increased, particularly when countries are included where nonexperimental options are relatively limited—a source also of some ethical debate [50]. Dollar costs may also be reduced when developing countries are involved [51]. The result of international studies may be more generalizable and more readily accepted by clinicians debating the applicability of a trial to their setting. While the international adoption of standards such as the Guideline for Good Clinical Practice aims to facilitate drug development by improving the acceptance of trial results by the regulatory bodies of differing countries [52], the actual conduct of such studies can still be challenging. Differing bureaucracies and approval methods for experimental studies can mean expensive or prolonged approval processes. In developing countries, the conduct of trials may require increased support for centers with little experience conducting clinical trials, and simplified and minimized information collection. Despite the sometimes difficult logistics, it is recommended that randomization remain centralized [53].

1.4.4 Know Your Audience, Know Your Market

Who Is the Audience? When developing a clinical trial, one must take into consideration the interested parties. First and foremost, there is the patient, who must deem the trial safe and attractive. There is the clinical investigator (and institutional review board), who must find the trial to be of sufficient scientific and ethical merit to allow accrual. There are the regulators, who may need to approve the trial for it to proceed and who will eventually need to approve an agent for nonexperimental use. And finally, there is the market, really an amalgam of the wills of patients and clinicians as influenced by competing therapies. While the term market connotes a mercenary purpose, the consideration of a drug's market is both worthy of time and compatible with the goal of optimal patient care.

Considering Current and Evolving Practice Clinical trials are not conducted in isolation. Rather, they become available to patients as an option alongside existing standard therapies. This imposes limitations on the experimental and control arms for a trial. For example, in many instances a patient commencing treatment for more than very mild rheumatoid arthritis (RA) would be a candidate for methotrexate [54]. Starting a patient purely on an experimental therapy could thus be deemed inadequate, and the experimental arm may need to employ both methotrexate and the experimental agent in combination. Similarly, it is considered unethical to unnecessarily delay treatment through the use of a placebo in the control arm of

a patient with RA [55]. Obviously, a trial that fails to consider these points is unlikely to be allowed to proceed, and even if approved may be unable to accrue.

Recognizing variations in clinical practice, a flexible treatment scheme has sometimes been adopted by trialists. In lieu of defining a specific control arm in a clinical trial, investigators may be allowed to choose the particular control or treatment arm that will be employed at their center [56, 57]. Such a trial is more likely to be attractive to a wider range of clinicians, as they may adopt local practices to the trial in question. This has obvious benefits for accrual and may enhance the generalizability of the study. On the other hand, such an open model may make it less clear what is being compared. For example, if the experimental arm contains several forms of therapy, a local investigator may not know if his or her standard regimen has been adequately compared to the experimental arm based on the primary analysis. While subset analyses may be performed, they are typically exploratory.

In addition to present practice, other concurrently operating clinical trials may impact on future practice and the ability to conduct a trial under development. First, a trial in the same population may compete for the finite pool of potential participants. Second, if a competing study is finished and found to be positive before the developing or ongoing study is complete, study completion may become impossible. The competing study may change the standard treatment landscape, alter investigator equipoise over the developing or ongoing study, and inhibit patient accrual. Patients will need to be informed of the evolving standard, and they may choose to avoid or withdraw from the trial.

Just as standards exist in clinical practice, methods of conducting clinical trials are largely standardized. While trial methodology is evolving, investigators and review boards may be uncomfortable with new methods. For example, in phase I studies in oncology, the common method of accrual is to admit cohorts of three to six patients at successive drug doses. Alternative methods, such as the accrual of one patient per dose level, or the continuous reassessment of the maximum tolerated dose using Bayesian methods have been advocated as potentially more efficient [3]. However, there is evidence that the implementation of new study methods is delayed, suggesting the discomfort of physicians or reviewing committees [58].

Considering Endpoints The choice of endpoint depends upon both the disease under consideration and the phase of clinical development of the drug. In congestive heart failure (CHF), for example, past successes in improving clinical outcomes have made it difficult to further improve results and to detect such improvements in phase III trials [59]. For drug development, this means that having an early, phase II assessment of activity is important to determine whether a drug should go on to phase III study. Given that phase II trials are intended to be shorter and smaller than phase III trails, using longer term endpoints such as hospitalization or mortality is unlikely to be practical. Surrogate endpoints are therefore considered for these phase II trials. While clinical endpoints represent measures of disease important to patient well-being or survival, surrogate endpoints are alternative endpoints that represent disease biology or a secondary clinical outcome and are intended to shorten the investigative timeline. To be valid, surrogates must correlate well with improvements in important clinical endpoints. One example of such a surrogate is brain natriuretic peptide, a neurohormone that predicts left ventricular function and prognosis and that has also become a diagnostic test [60]. While there is disagree-

ment about which surrogates are useful in CHF [61], the patient exposure to experimental therapy and the cost required by phase III studies dictate that an effort be made to use phase II studies, and surrogate markers can serve a useful role. Phase III endpoints must be more clinically relevant, in part because surrogate endpoints are not entirely reliable. In CHF, therefore, mortality is still a preferred measure of efficacy, although hospitalization rates and other secondary measures may be considered [62].

Endpoints once deemed of limited clinical value may gain importance through greater experience. Improvements in disease-free survival, an endpoint less concrete than overall survival, have historically not been regarded as sufficient to merit a change in clinical practice in many areas of oncology. More recently, analysis of accumulated studies has suggested that 3-year disease-free survival is an accurate surrogate of 5-year survival when administering adjuvant chemotherapy to patients who have had curative surgery for colon cancer [63]. The use of oxaliplatin in the adjuvant colon cancer setting was approved by the FDA on the basis of a disease-free survival benefit, and there is the potential to use such surrogates to shorten drug development time [64].

1.5 EXAMPLE IN DRUG DEVELOPMENT

To further understand the clinical trial process, it is useful to consider an example. The field of oncology has seen an increase in the number of experimental agents directed at specific disease mechanisms. These targeted drugs are sometimes considered to have the ability to prevent tumor growth while not actually causing tumor shrinkage (tumor response), and may be termed cytostatic agents. Typically, new drugs are first studied in patients with advanced, metastatic disease, and tumor response has been employed as a surrogate for clinically important endpoints such as survival. The challenge in studying cytostatic drugs is that they may not induce tumor response and may be less effective in patients with greater burdens of disease. Hence, useful drugs may be missed if tumor response is relied upon to demonstrate activity [65].

Such were the considerations during the development of marimastat, a matrix metalloproteinase inhibitor. Matrix metalloproteinases are a family of proteins that degrade extracellular matrix and thus facilitate the migration and metastasis of tumor cells and facilitate vascular growth. Preclinical work suggested marimastat inhibited this process [66]. Except for the first study, performed in healthy volunteers [67], phase I studies suggested a dose-limiting arthritis [68, 69]. These studies indicated doses for further work and suggested that achievable plasma levels were likely sufficient to achieve target inhibition.

Few single-agent phase II studies were performed, and tumor responses were rare [70–72]. With the understanding that marimastat might not show typical responses in tumors, a large study was performed with various tumor types to assess a surrogate endpoint, a change in tumor markers [73]. With the exception of prostate-specific antigen, the tumor markers that were used are not sufficiently associated with clinical endpoints that they are usually accepted as surrogates [65]. While an impact on tumor markers was suggested by this and another study [74], there was no clear evidence of improvement in any clinical endpoint.

Acknowledging the difficulty in detecting activity in metastatic disease, Miller et al. conducted a randomized phase II study in the adjuvant breast cancer setting [75]. This trial encountered musculoskeletal toxicity that prevented drug administration from being sufficiently sustained to warrant further adjuvant study.

Phase II data could thus be regarded as tenuous, but optimism was such that phase III drug development proceeded. In fact, for both the lung cancer and gastric cancer trials, there was no phase II data to support phase III efforts [76, 77]; the study in gastric cancer was based in part on pathological changes noted in a phase I trial [78]. The results of phase III studies were almost universally disappointing [77, 79–81], although minimal activity was seen in gastric cancer [76]. Development of the drug ceased.

It is unfair to be overly critical of the participants in such a story, but certain issues may be usefully considered. First, phase I studies may demonstrate some aspects of a drug's toxicity, but only with more patients and longer term follow-up will toxicity become clear. This became more evident in the phase II study in the adjuvant breast cancer setting, and flushing out the toxicity profile is another argument for phase II studies beyond looking for initial clinical activity. A resource-intensive phase III study would likely have been aborted in the same adjuvant situation. Second, surrogate markers can be misleading [60, 82, 83]. To be considered true surrogate markers, they must be biologically relevant, show a consistent and proportional relationship between a change in the marker and a clinically meaningful endpoint, and this relationship should be demonstrable in repeated studies [60]. Most tumor markers do not satisfy these requirements, and thus their use was probably not justified. That said, even markers directly in the biological pathway of a drug are not a guarantee of adequate surrogacy, as redundant and alternative molecular pathways may dilute or eliminate the relationship of the surrogate to a clinical endpoint. Unfortunately, an adequate biological surrogate test had not been established for marimastat. Proceeding to phase III studies based on uncertain surrogate markers was thus a gamble.

How does one decide when to carry out phase III studies in oncology for cytostatic drugs? This is still an evolving field. In terms of using clinical outcomes, the use of stable disease is being used by default, although there is modest evidence of a relationship between this and the more concrete endpoint of survival [84–88]. As response and even stable disease may be difficult to demonstrate in advanced malignancy, biomarkers are likely to remain relevant. Measuring direct effects on tumor is likely ideal, but many tumors are not readily accessible for repeat biopsy after treatment. In this instance, one might pursue changes in biomarkers in accessible tissue such as skin. There is still the hazard, however, that skin changes may not be representative of tumor changes. In either case, unless a similar drug has established a true surrogate relationship for the biomarker in question, investigators are left to establish the relationship, a very difficult task during the limited number of trials undertaken with a developing drug. In the absence of a validated surrogate or true clinical evidence of activity, the preclinical or clinical biological data must be compelling to proceed with large randomized studies. If it is, investigators might consider whether it is better to study the drug in the setting of earlier disease, perhaps in the adjuvant setting. While the benefit of a cytostatic agent may be more evident in this setting, larger treatment groups and longer follow-up are typically required to detect the small improvements in outcome often seen in early disease.

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