# Course outline: NROD60 Cognitive Neuropharmacology
## FALL: 2004

### *Course Details*

Instructor: Norton W. Milgram
Classroom and Scheduled Times:
Friday, 11:00 - 1:00, Room HW-408

### *Course Description*

1. General Purpose

The overall goal of this course is to provide a critical overview of the drug development process as applied to cognitive-modifying pharmaceuticals. The target population for the application of these drugs consists of (1) individuals showing impairment linked to age (age associated memory impairment); and (2) cognitive disorders associated with neuropathology, including Alzheimer's disease, Frontal- Temporal Dementia, and Parkinson's disease.

2. Topics Covered

The first part of the course will focus on the theory underlying treatment of cognitive dysfunction with pharmaceuticals, and the actual developmental process. Topics that will be covered include:

a. Use of drugs to modify behavior: lessons learned from the study of psychotherapeutic drugs.
b. Components of cognition. Before we can even consider drug design, we have to have an identifiable target system. The course will take a neuropsychological perspective, which attempts to distinguish various cognitive processes on the basis of underlying neurobiological structure.
c. Animal models of cognitive decline. What species and what types of tasks can be used to model human cognition? How do we model cognitive impairment.
d. What is the neurobiological basis of cognition? Can we identify the neural structure underlying memory? What is the contribution of various neurotransmitter systems to cognitive performance? Are their common underlying cellular substrates?
e. Clinical evaluation of cognitive function. What kinds of tools are used to evaluate cognition in humans? How reliable are they? Do the different tests measure different functions?
f. Mechanisms of action of putative cognitive enhancing therapies. How do the drugs work.
g. The entire process – from identification of a need to drug approval for treating cognitive impairment.

These topics will be covered using a lecture-discussion format.. You will all, therefore, be expected to do the assigned reading before class and to participate in class discussion.

### *3. Grades:*

Grades will be based on:

a. Performance on examinations - 50%
b. Class discussion - 15%
c. Term paper - 35%

a. Examinations

There will be a midterm and a final exam. The midterm will be worth 20$^{th}$ of the final grade and the final 30 percent. The final will be cumulative, and may include a take home component.

a. The term papers will deal with a specific intervention. The papers should summarize pertinent research on both human and animal models, discuss potential mechanisms of action and provide a critical overview of the potential effectiveness. The papers should be broken down by headings in subsections that include Summary, Introduction, Discussion, and References. The papers should follow the format of the Publication Manual of the American Psychological Association. The length excluding references must not exceed 15 double spaced pages.

Grading will be based on organization, clarity, scholarship (thoroughness of literature search).

The following are potential interventions that can be used for the term paper.

a. anticholinesterases - (aricept, galantamine, or rivistigmine)
b. ampakines
c. adrenergic agonists
d. antioxidants
e. cerebral vasodilators (hydergine)
f. gonadal hormones (estrogen and testosterone)
g. selegiline hydrochloride (l-deprenyl)
h. adrafinil and modafinil
i. secretase inhibitors
j. serontonergic agonists and antagonists
k. statins
l. stimulants (methylphenidate, amphetamines, caffeine)
m. nootropics
n. growth factors (NGF, BDNF)
o. neuropeptides (ACTH and vasopressin analogs)
p. vaccines
q. memantine
r. NSAIDS
s. Medium chain triglycerides
t. Docosahexanoic acid

### *Readings*


Bartus, R.T. (2000) The cholinergic hypothesis a generation later: Perspectives gained on the use and integration of animal models. In: Emerich, D.F., Dean, R.L, & Sanberg, P.R. (Eds). Central Nervous System Diseases: innovative animal models from lab to clinic. Human Press, pp3-45

Boller, F., & Duyckaerts, C. (1997). Alzheimer Disease: clinical and anatomic aspects. Chapter 41 in Behavioral Neurology and Neuropsychology. T.E. Feinberg and M.J. Farah (Eds). McGraw Hill, pp 521-544.

Citron, M. (2002). Alzheimer's disease: treatments in discovery and development. Nature Neuroscience supplement, 5, pp1055-1057.

Collie, A., & Maruff, P. (200). The neuropsychology of preclinical Alzheimer's disease and mild cognitive impairment. Neuroscience and Biobehavioral Reviews, 365-374.

D'Mello, G.D., & Steckler, T. (1996). Animal models in cognitive behavioural pharmacology: an overview. Cognitive Brain Research, 3, 345-352.

Harvey, P.D., & Mohs, R.C. (2001). Memory changes with aging and dementia. In: Hof, PR and Mobbs, CV (Eds): Functional Neurobiology of Aging. Academic Press, San Diego, pp 53-63.

Head, E., Milgram, NW., & Cotman, CW. (2001). Neurobiological models of aging in the dog and other vertebrate species. In: Hof, PR and Mobbs, CV (Eds): Functional Neurobiology of Aging. Academic Press, San Diego, pp 457-467.

Lane, M.A., Ingram, D.K., & Roth, G.S. (2002). The serious search for an anti-aging pill. Scientific American, (August) 36-41.

Lynch, G. (2002). Memory enhancement: the search for mechanism-based drugs. Nature Neuroscience supplement, 5, pp1055-1057.

Morrison, J.H., & Hof, P.R. (1997). Life and death of neurons in the aging brain. Science, 278, 412-424.

Olshanski, J., Haflick, L., & Carnes, BA. (2002). No truth to the fountain of young. Scientific American, 286 (June), 92-95.

Valenstein, E., (1998). Blaming the brain. The Free Press.

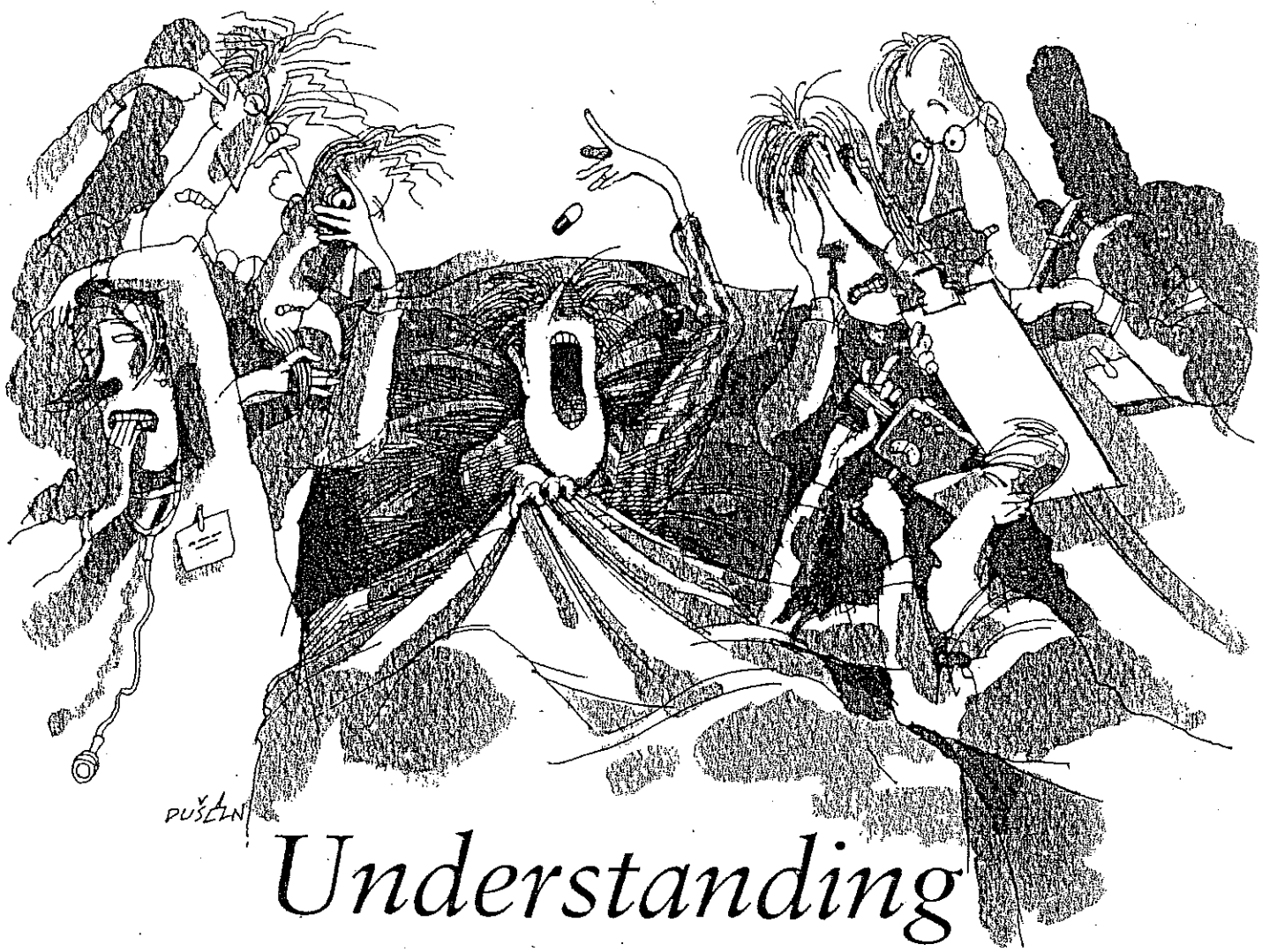
Van Reekum, R., Black, S.E., Conn, D., & Clarke, D. 1997. Cognition-enhancing drugs in dementia: a guide to the near future. Can J. Psychiatry, 42, 35-50.

Zivin, J.A. (2000). Understanding clinical trials. Scientific American, 282m 69-75.


Note – you're responsible to obtain your own copy of Valenstein. This can be done over the net from either ABE Books, Amazon (www.amazon.com) or Chapers – Indigo (www.chapters.indigo.ca) .

***Tentative Schedule***

| Date | Topic | Assigned Reading |
|---|---|---|
| 1 -Sept 10 | Introduction – The Process of Drug Discovery and Development | Zevin |
| 2 -Sept 17 | Use of drugs to modify behavior I –Historical background | Valenstein – Chapters 1 and 2 |
| 3- Sept 24 | Use of drugs to modify behavior - | Valenstein –Chapters 3 and 4 |
| 4- Oct 1 | Use of drugs to modify behavior I<br>Target systems for cognitive enhancing drugs<br>Cognitive and neuropathological correlates of aging and dementia- | Valenstein – rest of book<br><br>Harvey and Mohs |
| 5- Oct 8 | No Class | Collie and Maruff |
| 6- Oct 15 | First Midterm Exam | |
| 7- Oct 22 | Human Target systems – cognitive and neurobiological correlates of dementia and related neurological disorders | Boller & Duyckaerts<br>Morrison & Hof |
| 8 -Nov 5 | Animal Models | D'Mello & Steckler,<br>Head et al |
| 9 - Nov 12 | Clinical Assessment | Van Reekum |
| 10 -Nov 19 | Interventions: Symptom based | Bartus, Olshanski, Lynch |
| 11 -Nov 26 | Interventions: Mechanism based | Lane , Citron |
| 12 -Dec 3 | Final Exam | |




# *Understanding* CLINICAL TRIALS

*The journey from initial medical research to the bottle in your family's medicine cabinet is complex, time-consuming and expensive. Can the clinical trial process be refined?*

by Justin A. Zivin

One of the biggest stories in medicine of the past five years is surely the furor over angiostatin and endostatin, compounds heralded by some media reports as the cure for cancer (a premature claim, to be sure). The two substances—which dramatically reduced tumor size in a group of laboratory mice—made headlines for a few weeks in the spring of 1998 but then faded from public view.

Scientists, however, continued their slow, methodical study of the potential drugs. A year and a half later, in September 1999, doctors were at last ready to begin testing endostatin in humans. At press time, phase I of a clinical trial was under way in Boston, Houston, and Madison, Wis.; barring unforeseen complications, testing should continue through most of this year. But even if all goes smoothly and endostatin proves to be a safe and effective treatment, it will not be available to patients for several more years.

Another story that often makes the evening news is the promise of gene therapy, but almost half a century after the revolution in molecular biology began, no such treatments are available. Testing of gene

therapy is under way, however—and is currently the subject of intense scrutiny. The complaint this time is not about the slow progress of research but about whether the research is actually harming patients. In September of last year, a young man participating in a phase I trial of gene therapy for a rare metabolic disorder, ornithine transcarbamylase deficiency, died as a result of complications caused by the treatment. In the subsequent months, reports of additional deaths in gene therapy clinical trials have also been made public. Much of the discussion of these tragedies has focused on how the trials were run and whether misconduct on the part of the researchers could have led to the deaths.

The three-part clinical trial process required to judge the efficacy and safety of potential treatments is a major undertaking. The necessary trials may require more than a decade to complete and cost hundreds of millions of dollars. (For more detailed descriptions of the three phases of a clinical trial, see the boxes on pages 71, 73 and 75.) Trials that fail to show that a treatment works outnumber substantially those that prove that one *does* work, but both can cost the same. Although the precise numbers are not available because pharmaceutical companies do not like to report their failures, it is safe to say that thousands of drugs and medical devices have been evaluated in the past decade alone.

Most people know very little of how trials are conducted or what their scientific foundations are. Yet they may be asked to risk their health, and possibly their lives, to participate in a trial—often with little time to make weighty decisions. Furthermore, in recent years human trials have become more than just a way to screen new drugs. They have taken on an important role in the delivery of health care: many patients view participation in a trial as the only way to obtain experimental medications they consider potentially lifesaving.

Concerns about the way clinical trials are conducted have surfaced regarding the money, time and potential conflicts of interest involved. Do drug companies push researchers to report results in only the most self-serving way? Is it really feasible to explain all the potential risks to a patient (a requirement for securing his or her "informed consent") when the purpose of the trial is to learn about such risks? How do you balance the desire to test a drug candidate comprehensively with the desire to make lifesaving treatments available to patients quickly? The list of questions goes on. Under pressure from the public, the government and the companies funding medical research, clinical investigators are continually striving to cut the cost and length of the process—without sacrificing the quality controls set up to protect patients and to ensure that new treatments are safe and effective.

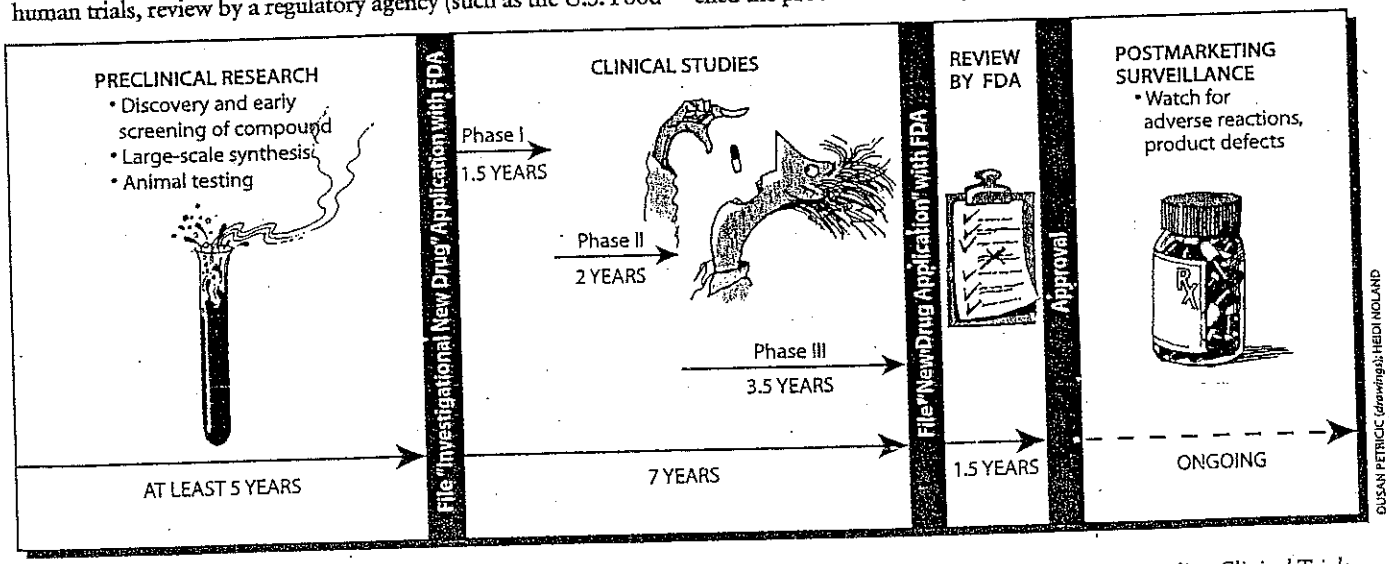
For more than 20 years, I have observed hundreds of clinical trials from a variety of perspectives: as a bench researcher, a clinical neurologist and an investigator in clinical trials. I have served as a consultant to the National Institutes of Health, the U.S. Food and Drug Administration and several pharmaceutical companies. I have also consulted for a contract research organization, a company that can be hired by drug firms to organize clinical trials. During these years, those of us involved in clinical trials have tried to develop improvements or alternatives to the traditional clinical trial. Some of these techniques may help resolve current dilemmas, but I believe that on balance the three-stage, randomized, controlled clinical trial remains the most reliable way to test new drugs and medical devices.

## Protecting Patients

A leading complaint about the current formula for testing experimental therapies on humans is the need for so-called blinded, controlled clinical trials. Ideally, neither physicians nor patients know whether a subject is part of the treatment group or the control group (which receives either a placebo or the best available proven therapy)—they are "blind" to whether the test drug is being administered. Complicating the issue is the idea of randomization, the practice of randomly assigning patients to either the test group or the control group. Because of this practice, patients often complain about being powerless "guinea pigs" for the far more powerful drug companies. They argue that patients whose only chance could be the latest, cutting-edge treatments should have guaranteed access to them.

If researchers somehow knew a drug candidate truly was a better treatment, however, there would be no need for a trial. It is scientifically essential that the division of subjects into the test or con-

TIMELINE FOR DRUG DEVELOPMENT typically spans many years, stretching from preliminary research in the laboratory through human trials, review by a regulatory agency (such as the U.S. Food and Drug Administration) and, finally, monitoring of drugs on the market. Efforts by the FDA and clinical investigators have shortened the process somewhat, but a thorough trial takes time.

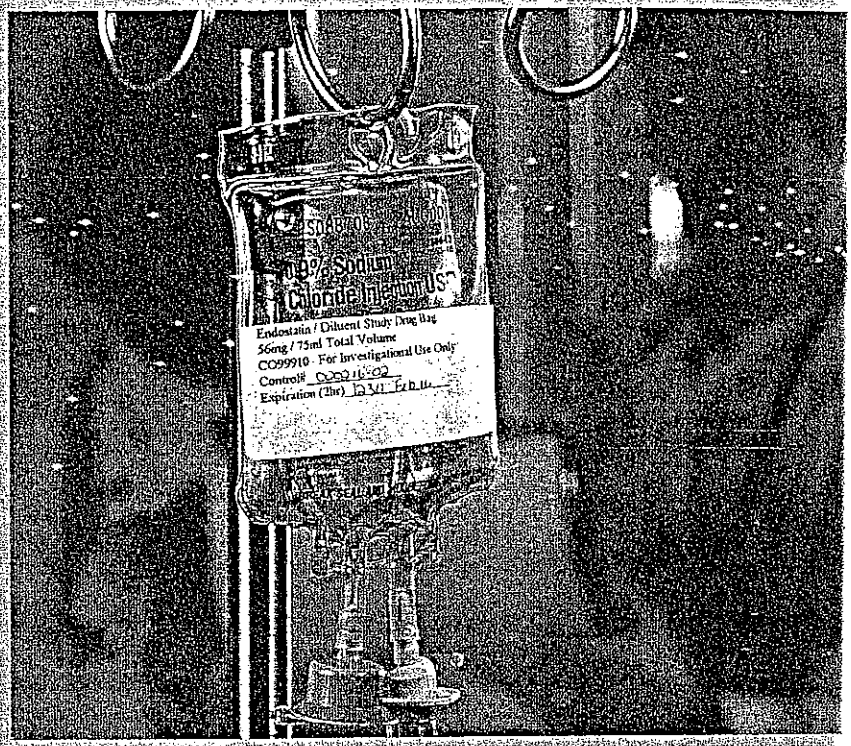


trol groups occur and that it be entirely random. Otherwise the final results will be skewed. If the test group were to consist mainly of patients for whom all other drugs had failed (and thus were more likely to be among the sickest patients), the drug candidate being screened could appear to be less effective than the placebo, even if it were not, simply because the patients receiving the drug started off in worse health. Conversely, if the leaders of the clinical trial consciously or unconsciously administered the test drug to healthier patients, it could appear to be more effective.

What is essential for science does not always make sense to patients, however, especially those with life-threatening illnesses. To protect patients from potential abuses and address their concerns, trial organizers incorporate many levels of oversight into their planning. First, doctors are bound by their ethics to provide patients with the best care possible, whether or not they are part of a trial. Physicians are never required to enroll people in an experimental study, and patients cannot be forced to join. When someone does decide to enroll, doctors must provide a complete explanation, both orally and in writing, about the nature of the study and all available information about the potential risks and benefits of participating. If patients or their responsible guardians agree to continue, they must do so in writing. This process is called obtaining informed consent. Patients always have the right to refuse to participate or to withdraw from a trial at any time.

But because of the impossibility of knowing in advance all possible side effects of an experimental drug, hospitals in the U.S. that run clinical trials operate Institutional Review Boards, or IRBs. This second level of oversight usually consists of a committee of caregivers, patient advocates and other interested nonprofessionals (for instance, lawyers or members of the clergy). The IRB must agree to a trial before it can begin at a site, and if the members become concerned about how a trial is progressing they can stop the trial at their hospital or request changes in procedure.

As an additional layer of patient protection, each trial usually includes a Data Safety Monitoring Board, or DSMB. This group of physicians and statisticians works independently of the sponsors of the drug trial and the scientific investigators. They monitor the trial, continually checking safety and peri-




ENDOSTATIN, a potential anticancer drug, is now in phase I testing at the University of Wisconsin Comprehensive Cancer Center.

## PHASE 1: Screening for Safety

Number of volunteers: 10–100 people, typically healthy

What researchers hope to learn: Maximum safe dose of drug

Typical length: 1.5 years

Typical cost: $10 million

In the first stage of a clinical trial, researchers gather information about whether a drug is safe to give to humans and, if so, how much they can tolerate. Administering a drug for the first time can be a frightening experience because the volunteers (who are usually perfectly healthy and are also usually paid) are taking a very real risk. The initial dose is typically very low, to minimize the possibility of a major reaction, but as doctors escalate the dose the potential for problems increases. If the possibility of extremely serious side effects exists, phase I testing is conducted in patients with the condition that the medication is intended to treat. Potential harm then is balanced by potential benefit.

Of course, before human testing begins, the general safety of the drug has been established in animals. But animals cannot express whether they are dizzy, nauseated or experiencing psychiatric symptoms; humans can and frequently do. And although such an outcome is extremely rare, volunteers occasionally suffer life-threatening side effects that were not apparent during animal testing.

The trial team monitors the participants closely, constantly observing their behavior and asking how they feel. Additionally, to spot problems early the researchers usually measure blood pressure and temperature, collect blood and urine samples, and monitor for any other danger signs warranted by the animal studies. The scientists also measure the level of drug in the bloodstream or tissues to determine how it is distributed in the body, how rapidly it reaches a therapeutic level and how the body eliminates the compound. When combined, these data help to determine the safe dosing regimen. —*J.A.Z.*

DUSAN PETRICIC (drawings); HEIDI NOLAND

odically evaluating other aspects. If necessary, the board can be unblinded during the course of the trial. If the DSMB finds that the treatment group is doing substantially better than the control group (or vice versa), the board can recommend the trial be terminated.

In some instances, physicians can offer experimental treatments to patients outside of a clinical trial. Therapies that have not been approved by the FDA can be made available to people who are extremely ill for what doctors call "compassionate use." But because such treatments have not been adequately tested in humans, recipients have no assurances that the drug or new medical procedure will help—or that it is safe. Moreover, the results of such experiments will not help anyone else, because they were not part of a properly designed clinical trial.

From what we now know about the phase I gene therapy trials that involved the deaths of some subjects, oversight committees can be misinformed [see "Gene Therapy Setback," by Tim Beardsley, News and Analysis, February]. In several of the trials now under investigation (several of which have been halted), the researchers did not inform the NIH of certain health hazards associated with the treatment—hazards they had observed previously either in animal tests or in other patients. (Most of the researchers had reported complications to the FDA, but that agency does not release data on trials.)

Such notifications—required by federal law—could have stopped the trials and prevented the deaths. Unfortunately, when researchers think they have discovered a "magic bullet"—a therapy that cures with complete safety—it may be hard for them to recognize the risks associated with any clinical trial. But the difficulties scientists will be most likely to encounter in developing gene therapies are similar to those considered commonplace in the testing of more traditional treatments. The recent deaths should remind all clinical investigators how vital it is to conduct our studies according to the well-established rules.

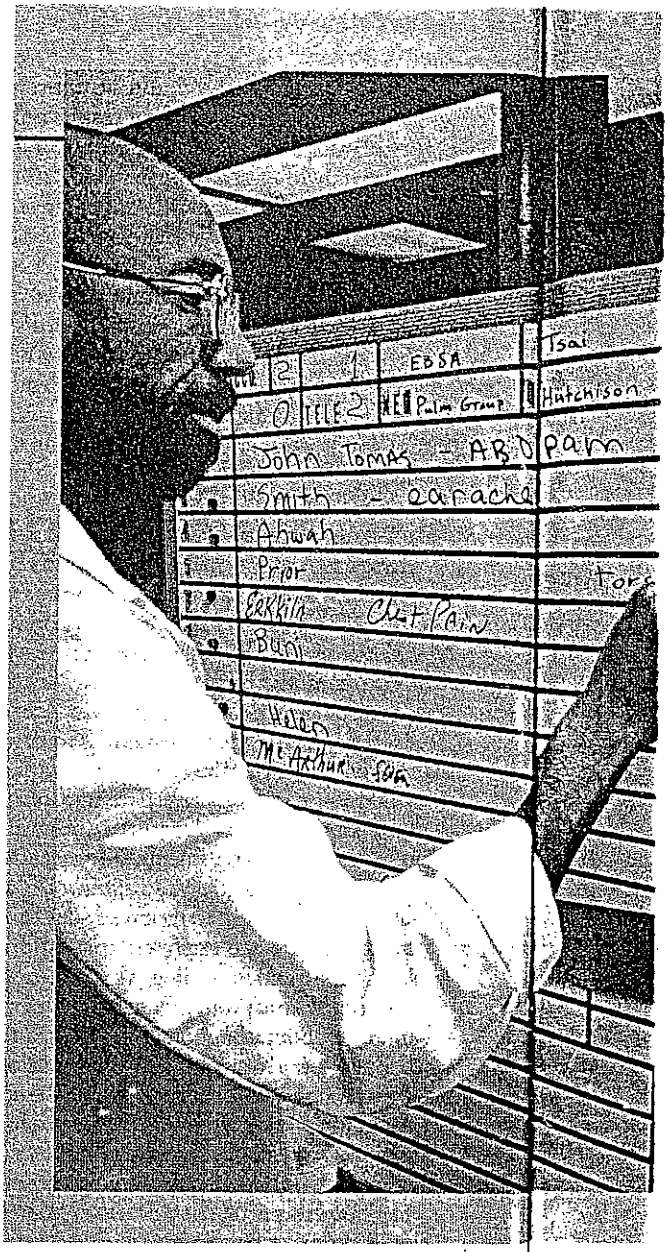
The public, physicians and pharmaceutical companies all agree that drug candidates should be tested quickly yet thoroughly so that useful new medications can be made available as soon as possible. The public's considerations are fairly clearly humanitarian. Physicians' motivations may be mixed, however. They want patients to get the best treatment, but they also benefit financially from entering patients into the trial—drug companies typically pay doctors for each new patient enrolled. And as the events of the gene therapy trials reveal, professional pride can be at stake as well. Pharmaceutical companies, of course, have a definite financial interest in moving trials along rapidly: the longer a trial runs, the more it costs them. In addition, a short successful trial allows a company to start selling its product sooner (and take advantage of patent protection on its drugs for a longer time).

## Speeding Up the Process

The rate at which a trial can be conducted depends predominantly on the number of participating investigators and patients. The faster the data are collected, the sooner researchers can begin to interpret the information. This is particularly true for therapies that may offer important benefits to only a relatively small number of patients and for those that provide only modest benefits for many people. For instance, taking aspirin daily prevents strokes every year in approximately 1.5 percent of patients who have suffered a previous stroke. Only by administering aspirin to a very large number of patients could researchers prove that such an effect existed. Although this benefit may seem small, aspirin costs only a few dollars a year, whereas the costs of taking care of one stroke survivor total about $50,000 a year. And viewed from a larger perspective, out of one million cases, some 15,000 people should benefit from aspirin treatment.

As a way to enroll as many patients as possible, as quickly as possible, trial leaders now run their studies at numerous sites around the world. More sites mean more patients and a diverse group of people who are more representative of those who will one day be taking the medication or using the medical device.

Despite the benefits of international trials, however, such efforts have come under criticism. Detractors argue that some drug companies take advantage of people in the developing world, testing new lifesaving therapies in these regions (particularly for HIV/AIDS) but then withdrawing access to treatment that is too expensive for most patients to purchase on their own. This issue, as troubling as it is, does not reflect a poor clinical trial design; who has access to medicine instead reflects current politics and economics. Ensuring that patients can get needed medicines that they cannot afford must and should be addressed by legal and financial means.




As trials grow in size, investigators accumulate increasingly vast amounts of information. The reports generated for just one patient frequently consume more than 100 pages of a notebook. The process of collecting such a mountain of data and checking it for accuracy accounts for much of a trial's price tag.

An alternative approach, known as the large simple trial, attempts to remedy part of this problem. In this method, physicians collect only the absolutely necessary details—usually just identifying information and a simple check-off list indicating whether the patient ended up better, unchanged or worse. The whole record can then be sent into the coordinating center on a postcard. Large


# PHASE 2: Establishing Protocol

Number of volunteers: 50–500 patients with the disease being studied

What researchers hope to learn: Who and how many people should be included in the final phase of testing; end points of trial; preliminary estimates of effective doses and duration of treatment

Typical length: 2 years

Typical cost: $20 million

The main goal of phase II testing is pragmatic: to find the experimental conditions that will allow the final phase of the trial to give a definitive result. (The purpose of a phase II trial is not, as some people assume, to prove that a drug candidate is an effective treatment.) In particular, researchers try to establish an optimal dosing regimen. One criterion that must be established immediately is the primary end point. End points describe unambiguous results that indicate exactly what the treatment can do. For instance, the usual end point sought when screening a new antibiotic is whether a patient is free of infection after treatment. Many ailments cannot be so readily cured, however, so an alternative end point might be whether the progression of, say, HIV/AIDS has slowed or whether the death rate from cancer has fallen.

Phase II marks the introduction of the control group to the trial. Almost all diseases are highly variable in their progression, with remissions sometimes occurring spontaneously. Researchers must be able to distinguish between a natural remission and the effects of treatment. Inclusion of a control group—which receives either a placebo or the best available therapy—makes it possible to perform this comparison.

Similarly, having a control group enables doctors to account for people in whom health problems unrelated to a drug candidate develop. For example, a medication being tested for treatment of high blood pressure might be suspected of causing nausea. But nausea can occur in just about anyone. Only if its incidence is significantly higher in the treatment group than in the control group will it be considered a problem.

Ideally, neither the physicians nor the patients know whether they are part of the treatment group or the control group—in other words, they are "blind" to the type of therapy being administered. During phase II, investigators work hard to ensure that the blinding procedure is successful. For instance, if a placebo pill is used, it is made to look exactly like the drug, and the patients are treated with either the drug or placebo in exactly the same way.

Yet in some cases, keeping a trial blind is simply impossible. If the test drug causes some kind of mild side effect, patients will quickly figure out that they are in the treatment group. Also, it is usually considered unethical to subject a patient to anesthesia and placebo surgery when surgical procedures are being evaluated. Researchers can compensate for the loss of blinding, however, and phase II enables them to work out how to do so before entering phase III. —J.A.Z.

PATIENT RECORDS must be carefully reviewed during phase II, when trial organizers refine the dose and duration of treatment to be used in phase III.

simple trials offer a far more economical plan for collecting data on huge numbers of patients; such trials routinely enroll tens of thousands of subjects for a small fraction of what it would otherwise cost. And with such large numbers of people, even small effects of a medication can be detected.

Large simple trials have a major drawback, however: they cannot be used to test a *new* drug candidate, because the side effects are unknown. Giving large numbers of patients an experimental medication that has never been screened for safety and has uncertain benefits is unethical. As a result, researchers typically run large simple trials to evaluate the relative effectiveness of known, approved treatments.

Progress in accelerating the clinical trial process is already apparent. According to a 1999 report from the Tufts Center for the Study of Drug Development, the average length of all clinical trials under way between 1996 and 1998 was 5.9 years—down from 7.2 years between 1993 and 1995. But even with timesaving measures in place, clinical trials still represent a large investment of time and money. So when the results are ambiguous, leaders of a clinical trial usually try to extract some useful information out of their hard work.

Often a phase III trial will show a trend in favor of a drug, but the effect will be too small to serve as statistically convincing proof. In many instances, additional trials give mixed results as well. For such cases, statisticians have developed methods for pooling data from all the previous trials to conduct what they term meta-analysis. Such evaluations remain controversial, however. The appeal of trying to salvage a valuable result from a collection of near-misses is strong. But questions remain about the validity of meta-analysis: the technique is subject to potential bias in terms of which studies were selected for inclusion and the comparability of those studies. The findings from a meta-analysis can be useful for interpreting a large amount of conflicting data, but the results are not generally considered definitive.

## Financial Dealings

Money—who pays for the research and who takes home the profits—looms over every clinical trial. For many years, the pharmaceutical companies have done most of the work of clinical trials themselves, hiring physicians to organize and run the trials, monitors to verify that the data have been collected accurately, statisticians to analyze the re-

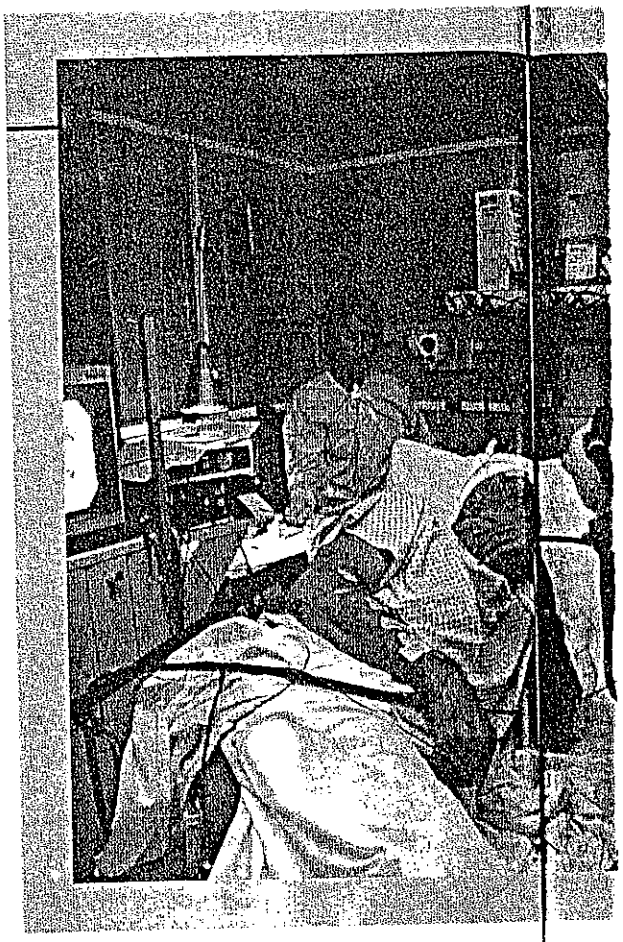
sults, clerks to enter findings into the databases, and a variety of support people to handle the administrative functions involved in coordinating such a massive endeavor. All of this is in addition to the local physicians and nurses who care for patients enrolled in the trial. The price tag for this enterprise quickly becomes substantial, running into hundreds of millions of dollars. As a result, no one should be surprised that drug companies want to recover their costs as expeditiously as possible.

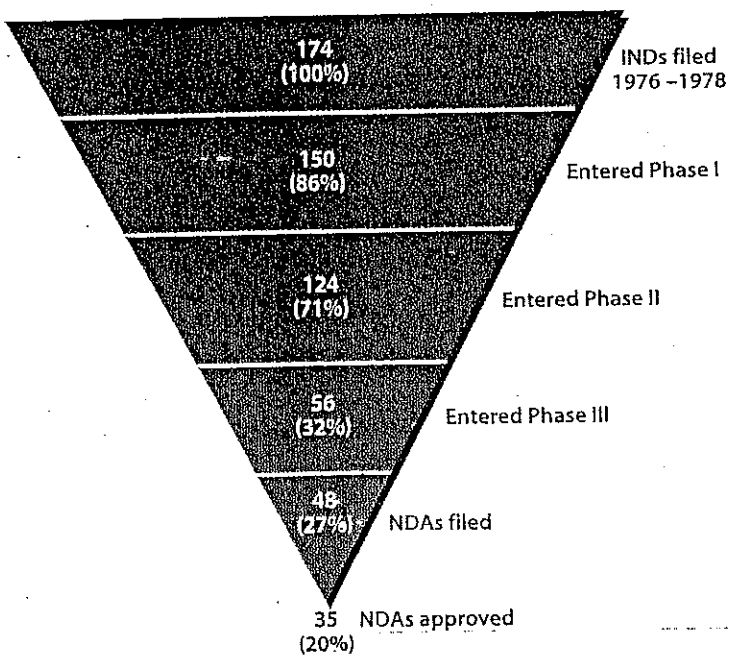
Stories of unethical behavior on the part of the pharmaceutical companies running clinical trials are relatively rare, but they do surface. Researchers involved in trials have sometimes complained that sponsoring drug companies restrict what they can report to their colleagues and the general public if a treatment appears not to work. One alternative to having the pharmaceutical industry finance so many studies is to have the NIH sponsor all clinical trials. Such an arrangement—which does happen on occasion even now—dramatically reduces the profit motive of the people conducting the trial and usually assures that the resulting studies will be of the highest quality.

But devoting tax dollars to research into new drugs, many of which will eventually result in large profits for pharmaceutical companies, is troubling. In the past, government support has been reserved for the trials of drugs that are unlikely to result in substantial profits or for highly speculative studies that are too risky for industry to attempt. For example, the NIH sponsored the trials indicating that aspirin reduced the occurrence of strokes in patients who had already suffered one. Although the number of patients who benefit from this finding is quite extensive, aspirin is so inexpensive that none of the manufacturers was willing to sponsor the studies, because the subsequent profits would not justify the costs.

A third approach to conducting trials has been tried in recent years: turning them over to a contract research organization, or CRO. These companies operate independently from pharmaceutical companies and are hired specifically for conducting clinical trials. The CROs generally do nothing but manage trials and often have the capacity to test various drugs in many countries simultaneously. Theoretically, then, CROs should be more efficient, and by relying on them drug companies ought to be able to reduce the costs of conducting large studies at numerous hospitals. Also, if a drug development program fails, the companies do not have to fire or transfer the sizable number of people needed to conduct the research.

Because CROs do not profit from the sale of pharmaceuticals, they should be less subject to conflicts of interest than the drugmakers are. They benefit financially only from the sale of their services. Presumably, then, companies will hire a CRO only if it conducts trustworthy trials that stand up to FDA scrutiny.






HEIDI NOLAND; SOURCE: "SUCCESS RATES FOR NEW DRUGS ENTERING CLINICAL TESTING IN THE UNITED STATES," J. A. DIMASI IN *Clinical Pharmacology and Therapeutics*; JULY 1995

DIMINISHING RETURNS are the norm in the clinical trial process. Only about 20 percent of Investigational New Drug, or IND, applications filed with the FDA make it to the final step, many years and many tests later: approval of a New Drug Application (NDA), which clears a treatment for marketing to the public.

In an attempt to minimize potential problems over financial conflicts, most medical societies and major journals now require from researchers a disclosure statement that describes how the work discussed was financed, along with any other details relevant to conflicts of interest. The U.S. government requires a similar declaration from investigators who participate in government-sponsored trials or from consultants involved in grant or regulatory decisions at organizations such as the NIH or FDA. Some people even argue that researchers who own stock in a drug company that supports their research should sell it. These considerations are relatively recent, and it is not at all clear yet what—if any—effect they have.

For the near future, the basic framework of clinical trials is here to stay, although efforts are under way to fine-tune the process. But the extent to which it can be refined has limits. I like to say that we can describe the conduct of a trial three ways: it can be trustwor-