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A Perspective on Clinical Trials for Citizens: Relatively Safe, Relatively Effective, Relatively Cheap

Clinical trials are in the news. Most scientists, and fewer citizens, have any familiarity with the complications, the history and the regulation of clinical trials. This is a lighthearted look at all three, not a definitive treatise. While expectations run high for new medical interventions, reality suggests caution, but not too much caution. Balancing the financial risk of novel therapies (both to develop and to apply them), their availability in a timely manner and the risk of adverse events requires compromises which are inevitably unacceptable to most of us. While we do not say it, we instinctively know that drugs can only be relatively safe, relatively effective and relatively cheap versus allowing disease to continue unabated. Without this relativistic approach, we will inevitably be disappointed. To expect safety and effectiveness in an absolute sense denies the fact that each time patients receive a new prescription, they are volunteering for a clinical trial of one. A better system for integrating information from all these "n of 1" trials might well be helpful, but we have no means yet of doing this.

Very few in the general public understand enough about clinical trials to make an informed decision about participating. A new organization has been created to help with this problem, and they have been hosting a few experimental programs to interact with the public. While one might be suspicious, this organization is not involved in recruiting subjects for clinical trials and does not itself conduct any trials. Its focus is "Education before Participation," to use their catch phrase. Learn more at www.smartparticipant.org, an activity of the Center for Information and Study on Clinical Research Participation (CISCRP), a first-of-its-kind non-profit organization founded in 2003, to:

Inform professionals, the media and policymakers about clinical research participation and what it means to be an active participant in the process,

Promote greater awareness and understanding of clinical research participation and the role it plays in public health, and

Facilitate more effective collaboration among all members of the clinical research enterprise.

There are many sources of information available to the public. Virtually all disease-specific non-profits have information on their web sites about trials related to their focus. A few of these are: diabetes.org; americanheart.org; lungusa.org; pdf.org; alz.org; nmss.org; cancer.gov; and aidsinfo.nih.gov. CISRP also accepts questions by telephone at 1-888-CISRP3.

In recent years, there has been much discussion about clinical trials, including disclosing them to the public (successful or not), publishing the science (successful or not), and the perceived or real conflicts of interest among participants, physicians, companies and Wall Street.

Particularly heated have been debates about medicines prescribed for children and whether their safety and effectiveness have been established beyond a reasonable doubt. Special concerns have been expressed regarding vaccines and antidepressants and their role in adverse events such as autism and suicide. Medicines approved by the FDA are to meet a goal described as safe and effective. These terms are relative, not absolute. What does risk mean in this context? Do we understand the differences between acute catastrophic diseases like heart attack or stroke and chronic conditions like Alzheimer's or diabetes? In this same context, do we think about social inconveniences like third-grade boys behaving badly, men losing their hair and women losing an interest in sex or having hot flashes? How are safety and effectiveness and cost to be determined across this spectrum of maladies? Where should our research dollars go? Are animals a good model for humans? How many humans should be tested and for how long? What should drugs cost? Who should determine this? Are they over-prescribed? Can we believe what we read? What can we expect? Why do drug ads on television end with a list of warnings and risks for products that are labeled safe and effective?

These issues are very complex. That fact alone suggests that we need a citizenry more aware of the issues so individuals can make informed decisions about their own health and that of their family and friends. There is now a great opportunity for individuals to learn more. The rapidly increasing number of institution-specific and disease-specific web sites allows patients to be participants in decision making like never before.

It is important to remember that the pharmaceutical industry is relatively new. There were very few drugs in 1950, and there were vaccines that changed the world. At that time, penicillin had been available for only five years. Our species muddled along pretty well for millions of years without the thousands of choices we have today. We worked hard to invent means to make life easier, to make food more readily available and to clean our air and water. As a result, we experience the unintended consequences of more cardiovascular disease and diabetes, and more of us are living long enough to suffer Alzheimer's, Parkinson's and the like. Yet we've made wonderful progress with medicines for polio, tuberculosis, diarrhea, hypertension, cardiovascular disease and a variety of

depressions. The first synthetic drugs to treat viral disease have been widely available for about a decade, less than the time we've had personal computers and cellular phones.

With scientific and engineering advances, the dramatic happens and then later seems obvious. After that it is a long, arduous task to improve things – making them incrementally better, faster and cheaper. As time goes on, the challenge becomes much greater as the standard to make something better seems to reach a limit. Think of the quality of recorded music, or the mileage per gallon for a car, or the speed of a commercial airliner. How much more can we squeeze out of a gallon of oil? Just as we are about ready to give up, the entire process can be disrupted by an advance. Think of phones that take pictures, receive email, are smaller than a candy bar and have a charge that will last for a week. We have parallels in the pharmaceutical industry. It has become harder and harder, and costs more and more, to make better and better drugs than we already have for many maladies. At the same time, we are in the midst of revolutionary advances in biology and chemistry that open up entirely new approaches. These advances are taking more time and costing more because our expectations are high and our standards for "safe and effective" are going up every year. But first, let's go back and list the complicating factors and then explore the history of testing new medicines.

COMPLICATING FACTORS

The nature of disease

It is important to appreciate the complexity of human disease and how that reflects on the design and expectations of clinical trials. In 1900, the five leading disease causes of death in the USA were (1) pneumonia, (2) influenza, (3) tuberculosis, (4) diarrhea and (5) heart disease. A century later the leading causes were (1) heart disease, (2) cancer, (3) stroke, (4) pulmonary disease and (5) diabetes. In the year 2000, adverse drug reactions and accidents fell between numbers 4 and 5. Note that the top four causes of disease a century ago all involved acute infectious agents, whereas the top disease causes of death today are progressive failure of endogenous organ systems. This makes an enormous difference because in the first case, an external cause is well defined, suggesting a strategy for attack with vaccines and antimicrobials. In the progressive failure of internal systems, separating cause from symptoms has turned out to be far more challenging. Because it occurs over a longer period of time, there is often no defining moment when the process has begun. Thus, diagnosing the chronic difficulty, or preventing it in the first place, remain areas where much improvement can occur. Science now has the tools to address these issues, but the public seems unsure of how to pay for the effort.

It is also important to keep in mind that for over two-thirds of the world's population, or four billion people, infectious diseases remain the top killers, just as they were in the USA and Europe in 1900. We all understand the drama of AIDS in Africa, but we should be reminded that malaria kills 20,000 to 30,000 humans each week.

People are like snowflakes – all different

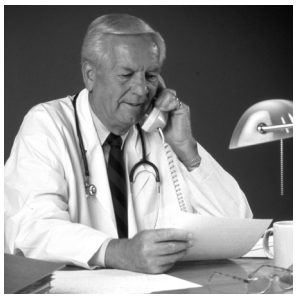
While disease varies, people also vary dramatically and this substantially confounds the design of clinical trials and interpreting the results. We are getting closer to the possibility of designing, or at least selecting, therapy for each of us as individuals (a concept known as pharmacogenomics), but except for very few examples, this remains impractical today. In this new view of things, we expect not to simply treat chronic disease by symptoms, but to look more deeply at underlying mechanisms. Diseases that are treated today assuming a uniformity of both disease and patient will in the future be viewed as variable, allowing for individual therapy as understanding is gained. We not only vary genetically, but we vary with respect to time and lifestyle as well. For example, some 1.4 million Americans today are reported to be in their 90s, and 60,000 or so are over 100. Per individual, seniors consume five times the drugs of working-age adults, although the definition of working age seems to be rising for many.

The old phrase "you are what you eat" is also very relevant today. Diet has a very clear influence on the biochemistry associated with chronic conditions. We eat chemicals. Drugs are chemicals. The reaction of our liver and our gut to both our breakfast and our various prescriptions are closely coupled. Thus, so-called "food effect" trials are now a serious cost-driver, to say nothing of the combination of prescription medicines with botanical products, which now take up much shelf space at the supermarket.

Life-threatening versus inconvenient, chronic versus acute, rich nations versus poor

I've already hinted at these topics above. They all suggest a need to prioritize. Who should decide?

Who determines what is safe enough? Who determines what works?



This is the big one! There is constant pressure along the stress lines between patient groups, the pharmaceutical industry, the FDA, elected politicians and Wall Street. The stress will continue because there is no solution. Cost tolerance and risk tolerance will always vary. The Holy Grail of safe and effective is a relative, not an absolute concept, and it must be coupled to both cost and availability. How safe? How effective? When? Who pays and how much?

CLINICAL TRIALS VARIABLES

Is animal testing viable? How much is required?

In earlier days, it was not uncommon for scientists and physicians to experiment on themselves or on others without obtaining permission from anyone. Today we expect some safety and efficacy studies in laboratory animals before receiving permission to dose a human subject. It is sometimes said that we have more effective medicines for tumors in mice than we do for humans. This begs the question of what is an appropriate animal model of human disease? Should animals even be used at all? And if so, how much work should be done before the first human dose?

How long should a trial last?

Treating an infectious disease is relatively straightforward, but how do we treat chronic conditions like depression or diabetes? How long should a human trial proceed before a new

drug is approved? Is five years enough for a drug that will be used daily for 30 years? Or is five years too long to wait? Is a surrogate marker for disease acceptable, or must we wait for the disease itself to become manifest?

How many participants should be enrolled?

The number of study subjects required to arrive at acceptable statistics is a matter of opinion, not science. For political polls we sample 1,000 Americans to draw conclusions about 300 million of us. If a drug is to have two million prescriptions written every year, should we test it in 1,000 or in 5,000? How many of those should be smokers? How many should be obese? How many should be of Asian or African descent? How many should have some co-morbidity with the disease under study? How many should be prescribed simultaneously with other drugs? How many should be regularly taking botanical products or exercising regularly or working at a high-stress job? In the end, the number of individuals in any given cohort will necessarily be relatively small. Thus, surprises after approval are not uncommon.

How much should be disclosed to the public?

There has been a flurry of discussion about disclosing the results of clinical trials to the public. We are in the age of transparency where everything must be disclosed, and full disclosure is now underway. The unintended consequence of this is that without filters, most of us have no time to digest all that is disclosed to us and we toss much of it away. Nevertheless, having the information available is a good thing. We will learn how ambiguous much of the medical arts remain, and the public will perhaps now have an opportunity to understand clinical trial design and better evaluate risk versus benefit. For example, there has been much concern published about the risk of suicide in depressed youngsters. But who is at risk without medication? Who is at risk with medication? Is the medication reducing risk in some but increasing it in others?

HISTORY

Let's now go back in history to see how all this started. There are biblical references to what might be called clinical trials. Chapter 1 of the Old Testament book of Daniel describes some tests on a group of young Israelite men of noble lineage in the court of King Nebuchadnezzar II. He ordered them to be on a strict diet of meat and wine for three years. At Daniel's request, a select group was given vegetables and water as an alternative. After ten days, the group given the alternative diet appeared to be more fit than those sticking to just wine and meat. One can thus see some early wisdom to the effect that: (1) kings are not always right; (2) it's smart to have a control group before coming to a conclusion; (3) it's smart to limit members of a test cohort in some fashion to control variables (i.e., only Israelite males were tested); (4) we all should become vegetarians; and (5) it's important to do a benefit-versus-risk assessment for wine at different levels of consumption. It is clear from this that even circa 600 B.C. the basics for a reasonable trial were established.

Scurvy

The most widely-cited first serious clinical study is that reported in 1753 in a book entitled *Treatise of the Scurvy* by Scotsman James Lind. Lind's interest in this disease was stimulated by Lord Anson's account of circumnavigation of the globe during which some 380 of 510 crewmen on one of Anson's ships succumbed to the disease. At the time, there were rumors but few facts. Lind set out to set the record straight "upon attested facts and observations, without suffering the illusions of theory to influence and pervert the judgement."

Lind's work was totally empirical, but it was a controlled set of observations, not casual. He had no idea of any theory that could be behind the choice of possible treatments. At the time, nothing at all was known about organic chemistry or the nature of Vitamin C. The name ascorbic acid of course derives from Lind's work in that the adjective scorbutic is defined as: "of, pertaining to, resembling or afflicted with scurvy." The first animal model of scurvy was demonstrated in 1907 by Norwegians Axel Halst and Theodore Frolich who demonstrated the disease could be induced and reversed in guinea pigs – an interesting case where human trials came before animal research. Vitamin C was isolated in 1928 by two independent teams led by Albert Syent-Gyrogyi and Charles King. Its molecular structure was determined by Walter Haworth, and it was first synthesized in 1933 by Tadeus Reichstein. It is the first vitamin to be prepared. While we tend to rush to judgement today about things clinical, it took 42 years for Lind's demonstrated effective treatment for scurvy to be adopted by skeptical authority and 180 years to isolate and prepare the responsible agent.

In 1795, the British Admiralty finally sanctioned the use of lemon juice, and by the early 1800s, scurvy had virtually disappeared from the British navy. Scurvy was common among soldiers in the American Civil War, and the problem appeared again on the Robert Scott South Pole expedition in 1902.

Vaccines, the story of smallpox (aka variola)

It was long observed that contracting some diseases was protective against repeat cases for those lucky enough to survive. As early as the 11th century, the concept of variolation was described. Healthy people were intentionally exposed to material collected from the sick, for example by drying scabs from pox and blowing the resulting powder into the nose of those uninfected. Apparently this practice was quite common through the 18th century, even though a side effect of the treatment was death in 2 to 3% of those treated. We all have heard the story of Edward Jenner (1749-1823), the English physician who noted that milkmaids who developed the related but less devastating disease, cowpox, were then immune to smallpox. In short, Jenner used the variolation idea, but collected the infectious material from milkmaid Sarah Nelms who had cowpox, and applied it to a healthy 8-year-old boy. The boy did contract cowpox but recovered in several days. Jenner then exposed the boy to smallpox. This was in 1796, and the boy was James Phipps, the son of his gardener. Suppose the experiment did not work. What would the parents say? Which law firm would they employ? Are one boy and one milkmaid sufficient, or should hundreds have been chosen? We know the history. It worked.

Perhaps the most dramatic tale of global diffusion of clinical trials began in late November 1803 when physician Francisco Xavier de Balmis sailed with a team of assistants and 22 orphan boys to Spain's colonies in the New World. The boys were to carry the vaccine and they were inoculated in

sequence to preserve the previous treatment in vivo, given that there was no refrigeration alternative in 1803. The expedition spread knowledge through the Caribbean and South, Central, and North America as far as present-day Texas. The results were spectacular and the expedition continued across the Pacific Ocean in February 1805, this time with 25 Mexican children aged 4 to 6, destined for Manila. The children kept the viruses alive in pairs (one a back-up) for ten days or so. The arm of one would supply the inoculate to be passed on through a cut on the next. A sea voyage of several months was thus feasible. The expedition returned to Spain in 1806, an unqualified success. This tale has the potential to inspire a movie, and it did inspire a work of historical fiction, *Saving the World: A Novel* by Julia Alvarez (2006).

Jenner invented the word *vaccine* from the Latin *vaca* for cow. It took time for this new technology to be adopted. Variolation continued until at least 1840, paving the way for all of immunology. Smallpox was not declared defeated until 1980, the last epidemic case having occurred in Somalia in 1977. Vaccination of military recruits ceased in 1990, but then interest arose again in the fall of 2001 with concern for bioterrorism. The World Health Organization estimated that as many as 500 million died of smallpox in its last century. While it took nearly 200 years to fully apply Jenner's idea globally, no one can sensibly argue that this early clinical trial was a mistake. Vaccines against both malaria and HIV are currently in clinical trials. A recent book, *The Life and Death of Smallpox* by Ian and Jennifer Glynn, is a good historical account (Cambridge University Press, 2004).

Diabetes

One of the more dramatic events in medical science occurred in 1922 when Banting and Best injected crude extracts of pancreas into Leonard Thompson, a 14-year-old boy dying of diabetes in a Toronto hospital. As a result, the boy lived another 13 years. Some 80 years later we have a variety of insulins, and clinical trials continue for inhaled insulin and pancreas islet transplantation. Therapy based on stem cells is also looking feasible, although it likely will take a decade or more of further research. Similarly, we now have numerous therapies for so-called type II or late-onset diabetes, which is at epidemic stages.

There are special connections to diabetes in Indiana. Eli Lilly was first to adopt the Banting and Best results to commercial practice, and Pfizer is producing insulin for inhalation in Terre Haute. Roche Diagnostics in Indianapolis and Bayer in Elkhart are leaders in home glucose test meters available in every pharmacy. BASi in West Lafayette has worked on technology behind glucose sensing for 30 years and even today is giving contract research support to clinical trials for Type II diabetes therapy.

Sulfa Drugs and Chemotherapy

Through most of our history, treatments for disease involved natural remedies varying from prayer to witchcraft to copper bracelets to wishful thinking. As we have seen with scurvy, vaccines and diabetes, solutions could be found in natural science as well. The idea that synthetic organic compounds could have utility is only a century old. Once the germ theory of disease was put forth in the late 1800s, it was not long before the idea of killing these microbes in vivo with chemicals came to light. (I like to describe these as chemical warfare agents.) The key historical figure here is Paul Ehrlich. He coined the terms "chemotherapy" and "magic bullets" to define what evolved into the modern pharmaceutical industry. We all remember from high school biology that microbes could be stained with dyes so we could better see them under a microscope. Ehrlich opined that the selectivity some dyes displayed suggested they could be used to kill organisms with some selectivity, thus "magic bullets that seek their targets of their own accord." Today we'd call them smart bombs. Magic bullets originated in the Carl Maria von Weber opera, Der Freischütz, when the devil traded a man's soul for magic bullets, guaranteeing victory in a marksmanship contest to make a favorable impression on a woman. In April of 1910 Ehrlich announced the use of Salvarsan against syphilis. It was the 606th agent he tried; today we might try 100,000 or more. Syphilis was the HIV of that day, and the drug was protested as a morally unacceptable alternative to chastity and monogamy. Ehrlich got many others thinking.

Another seminal figure in this effort is Gerhard Domagk who worked at I.G. Farbenindustrie at Wuppertal-Elberfeld, Germany. Domagk is a fascinating character who served in World War I, was wounded, and completed his medical degree in 1921. During World War I, and perhaps during all previous conflicts, more battlefield deaths resulted from infection than from the immediate wounds from bullets or swords. In fact, the infections often occurred simply from the poor living conditions of infantry in the field.

Domagk followed Ehrlich's notions and screened many dyes for their ability to kill streptococci bacteria growing in dishes. He then tested compounds that passed this screen in mice. A key breakthrough occurred in late 1932 when a red dye was tested and found not to be effective on plates. Domagk, for reasons unknown, decided to test the die on mice that had been dosed with virulent streptococci. Of the total of 26 mice, all 14 of the control mice died within four days, and all 12 that had been treated survived. The dye was named prontosil. Later it was discovered in France that it was not the dye itself, but a metabolite of the die, sulfanilamide, that was responsible for the benefit. Domagk moved quickly to humans, successfully treating his only daughter who was suffering a severe streptococcal infection. Domagk's drug development approach is basically what is still used today, albeit with far more elegance. We make an agent, test it in vitro, move to animals and then to humans. As in the prontosil case, there can be many surprises and often the mechanism of action of the drug is not what was originally supposed.

Back then, when a benefit was dramatic against a catastrophic disease, carefully controlled studies and statistics didn't seem to matter a lot. The focus was always more on the benefit and less on the risks of any treatment. The greatest risk was that the disease would continue and be fatal. Domagk was awarded a Nobel Prize in Medicine in 1939, although he was not able to receive this acclaim until after World War II. I highly recommend *The Demon Under The Microscope* by Thomas Hager, Harmony (2006), 340 pp., which recounts the history of sulfa drugs.

Penicillin

In the early 1940s, research on penicillin was undertaken at Oxford University by Howard Florey, Ernst Chain and Norman Heatley. The observation of an antibacterial exudate from mold was first made by Alexander Fleming in 1928, but Fleming was not a chemist. He was unprepared to isolate the active component and dropped the matter. The common

stories about the discovery of penicillin are largely romanticized and inconsistent with the facts. (This has happened often in medical science and might be the subject of another essay.) The Oxford group treated a few mice and got to work on patients relatively quickly. Then, as now, in the UK it was less controversial to experiment on humans than on mice. Penicillin was in such short supply that urine from the clinical study subjects was collected and the excreted penicillin was re-isolated and used again. At the time, it was possible to produce the antibiotic only by mold growing on the surface of shallow dishes. At one point bedpans were used. It was not until deep fermentation was perfected in the United States that supplies ramped up sufficiently for it to be a major factor in reducing battlefield deaths in World War II. This new fermentation technique involved blowing in sterile air while agitating with a motion not unlike a modern washing machine. Pfizer became the major volume supplier out of their Brooklyn, New York facility. (I have a kinship with that facility, since they helped support me with a high school science fair project on antibiotics in 1960.) A fascinating book on the penicillin story was published in 2004 (*The Mold in Dr. Florey's Coat* by Eric Lax, Henry Holt, New York).

Syphilis

Paul Ehrlich developed early magic bullets to combat syphilis, but they were hardly safe and effective by modern standards. Penicillin was the first real cure.

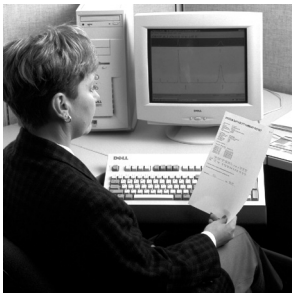
The history of clinical trials is not lacking bad examples. As with anything that is now a highly regulated bureaucratic process, there are good reasons the rules came into being. Well into the 1960s, treatments were often tried first on prisoners or the mentally retarded, providing the test subjects with no information at all. There is no more dramatic example of ethical lapses than the Tuskegee syphilis experiment that lasted from 1932 to 1972, and was fully sanctioned by the U.S. Public Health Service (PHS). Amazingly, President Clinton officially apologized for this in 1997. Curiosity can have evil ramifications. Here we had 399 black men with syphilis who were observed as their disease progressed and then were eventually autopsied. The purpose of the experiment was never explained truthfully. Participants were enticed with promises of medical care that was not provided. Care was even faked. When penicillin became available, it was withheld from these poorly educated men. Amazingly, hospitals, doctors and nurses from the African-American community played a role. All of this is documented in a book, *Bad Blood: The Tuskegee Syphilis Experiment* by James H. Jones. I mention this to be sure we all understand what humans are capable of when we complain about being hindered by regulations.

There are many historical examples of trying things on human subjects, as well as on other mammals, just to see what might happen. Today we'd hope that experiments are carefully designed and have a clear and beneficial purpose. Let's now take a look at the modern way by considering current regulations.

REGULATION OF CLINICAL TRIALS

Physicians are sworn to do no harm according to the Hippocratic Oath. This concept opens up a number of ethical difficulties with clinical trials when the experimental therapy is ambiguous with respect to safety, effectiveness and the use of placebos. The matter was really brought to a head at the Nuremberg trials following WWII when revolting human experimentation on prisoners was revealed to have taken place with the absence of any ethical considerations. This resulted in the first rules formulated to guide human experimentation, the Nuremberg Code of Directives for Human Experimentation issued in 1947 (*Nazi Medicine and the Nuremberg Trials: From Medical War Crimes to Informed Consent* by Paul Julian Weindling, Palgrave Macmillan, New York, 2004). Later, an International Conference on Harmonization (ICH) met and further refined the principles, issuing the Declaration of Helsinki in June 1964, and updated several times since. Here the concept of informed consent was defined, requiring that each potential subject in a trial be made aware of the aims, methods, potential benefits and potential risks or discomfort of a trial. Guidelines for the code of practice for trials were developed and are known as GCP, good clinical practice. Furthermore, the concept of an Institutional Review Board, or IRB, was established. This is an independent group who reviews the design of the trial and the information that will be presented to study subjects, enabling them to make an informed decision about their participation.

Development of U.S. Drug Law



The initial law was the Food and Drugs Act of 1906, which required that drugs meet some standards of composition (i.e. strength and purity) in view of the fact that many products were being sold with improper or fraudulent labeling, similar to many botanicals today. Harvey W. Wiley, Civil War veteran, Hanover College graduate and the first chemistry teacher at Purdue University, was the key force behind this act and behind the founding of the FDA as a government agency. The Federal Food, Drug, and Cosmetic Act of 1938 was far more comprehensive and for the first time required that manufacturers prove the safety of a drug before it could be brought to market. This legislation was delayed for five years, and passage was ensured only when a tragedy occurred wherein 107 people died from a poisonous ingredient in a sulfanilamide formulation. Surprising as it may seem today, it was only with passage of the Durham-Humphrey Amendment in 1951 that there was any requirement at all for drugs to be labeled "for sale by prescription only." The Kefauver-Harris Drug Amendment of 1962 was stimulated by the horrors of thalidomide in Western Europe. It was here that the concept of "safe and effective" was codified and applied retroactively to all drugs introduced after the 1938 FDC Act. The 1962 amendment required informed consent for trials, and also that advertising in medical journals be complete with respect to both risks and benefits. While not a new law, in 1981 the FDA issued more detailed regulations on protection of human subjects, informed consent and standards for IRBs that refined the GCP requirements.

Clinical trials are described by various terms, including first time in man or human (FTIM, FTIH). In the industry one hears of food effect trials, drug interaction trials, pivotal trials, bioequivalence trials, and so forth. Generally the process is

phased, with later phases involving larger numbers of study subjects. The FDA web site, www.fda.gov is an excellent source of information. The four major phases of clinical trials are delineated there, although the definitions are not highly precise. For any given new molecule, there often will be multiple trials within each category with somewhat different objectives.

•Phase I. First studies in people, to evaluate chemical action, appropriate dosage, and safety. Usually small numbers of participants are enrolled and typically there is no comparison group. These studies generally do not test efficacy and thus often require only a day or two. The study subjects are expected to be healthy individuals, although for oncology drugs this is most often not advised.

•Phase 2. Provides preliminary information about how well the new drug works and generates more information about safety. This phase usually includes a comparison group and patients may be assigned to groups by randomization. The numbers can be small (10) to modest (250).

•Phase 3. Compares intervention with the current standard therapy or placebo to assess dosage effects and safety in a larger population (hundreds or many thousands, depending on the nature of the disease).

•Phase 4. Post-marketing surveillance evaluates long-term safety, and sometimes effectiveness, for a given indication, usually after approval for marketing has been granted by the FDA. Many of us feel that this area should be improved. After all, every new person prescribed a drug is, with some small level of risk, participating in a clinical trial. It is fair to say that the better we are at Phase 4, the more sensible it is for provisional approvals at Phase 3. When we have better national standards for healthcare information systems, tracking experience with marketed drugs will become easier.

As for Daniel and the young Israelites of King Nebuchadnezzar, each trial involves inclusion-exclusion criteria to improve the analytical precision for the given number of study subjects selected. These criteria typically involve age, sex, weight, racial origin, smoking and specific components of medical history. With respect to the latter, one frequently hears the terms morbid, morbidity and co-morbidity. We refer here to the condition of being diseased. It is not unusual to find more than one condition simultaneously, that is, co-morbidity. This is especially common in the elderly. A depressed, alcoholic person with hypertension, arthritis and Type II diabetes would be an example. Suppose this individual is already prescribed three other drugs? Normally such an individual would be excluded from all early trials of a new drug candidate, with the goal to reduce the number of variables. On the other hand, if only nonsmoking men are included, how will we know anything about safety and efficacy for women? What about pregnant women? Or children? Until quite recently, women were often not fully considered in early trials. Their biochemical cycles and the possibility of pregnancy were rightly viewed as complications. The mistaken notion of women being the gentle sex or being unfit for infantry combat suggested they were not tough enough to participate. We now know better.

The same issue for children became very heated over the last decade. Understandably, there has been great reluctance to include them in many trials. The informed consent principle is only one of the problems. On the other hand, millions of prescriptions are written for children. What are we to do? Sometimes we forget that in 1954 the largest voluntary clinical trial in history took place when some 650,000 children (ca. seven years old) were given a series of three shots and thus became Polio Pioneers. Would this even be possible today? The FDA has encouraged pediatric clinical trials for new medicines by offering an extension in exclusivity for six months. It is now very clear that children are not small adults. Their systems are different, and often safety in adults does not guarantee the same in children.

LIES, DAMNED LIES AND STATISTICS

Few drug development surprises can be as devastating to both healthcare promise and company finances as toxicity problems that show up only under a very rare combination of conditions. These rare adverse drug reactions are referred to as idiosyncratic toxicity. Because of variations in human drug-metabolizing enzymes and protein drug transporters, there may be no apparent evidence of such problems during preclinical safety studies in laboratory animals. For one thing, animal models are purpose-bred and have a much smaller genetic, dietary and age variation than do humans. Such problems are also unlikely to show up in all but the largest clinical trials, but if the side effects are serious, it can result in product withdrawal. The industry is challenged to find a way to predict such problems, but that becomes challenging when these events occur in only 1 out of 10,000 or more patients. How can 10,000 be tested prospectively to protect one of them? If this is the best therapy, should it be withdrawn from the market to the dismay of 9,999 patients? In the recent case of Vioxx, the problem appeared in roughly 100 out of 10,000 and the drug was withdrawn in the face of other medicines that appear to be safer. Many do not agree with this decision. There is no right answer. When you see a statement like, “roughly 100 out of 10,000,” don’t believe it. Don’t believe me. It is never so simple. One must have some context regarding age, dose, condition, time, etc. It’s wise to read the original literature and never rely on a newspaper summary.

Looking at the other side of the same coin, there are clinical trials where fabulous results are obtained in a few patients with terminal disease, while there is no positive result in the vast majority. Should the average disappointing result keep the drug from those individuals for whom the results seem miraculous? The pessimist will say the trial failed. The optimist will say we must find out why it worked so well in some. The moralist will say it should be approved anyway if there is no alternative for this group of patients. The economist will say the cost is too high for so little gain. Bias and spin are not only for politics.

In the days of Lind, Jenner, Ehrlich, Banting and Best, Domagk and Florey, the trial results were dramatic and unarguable. Good things happened. There is bias in the fact that these people are remembered and can be found using Google. Experiments that work are favored over the larger number that didn’t work. Today the challenges are much greater and the results are much less clear. The pioneers did not consider random, multi-site, double-blind, placebo-controlled trials monitored for conflicts of interest. Often the "end points" in a modern trial are less easily quantifiable than for smallpox. Today we also look deeper at risk, far below the 2 to 3% of deaths that were apparently tolerated for variolation. We

also consider whether the physicians or participants might hold an equity position in the company developing a drug or device. How are we to know if an antidepressant really is working? How do we quantify a suicidal thought, or even a bad dream? There is nothing physical to measure equivalent to blood pressure, viral load or cholesterol. In the cases where treatment is available and the disease is catastrophic, there is no moral justification for withholding treatment from a placebo group. (See sidebar.) Thus the trial will compare a current standard practice to the experimental therapy. But suppose the experiments don't work, or even cause harm? How soon should the physicians and patients be unblinded? Who should decide? What should be published? There is a long-standing publication bias for scientific and medical journals. There is even bias in selecting experiments. Scientists tend to design experiments to prove their hypotheses and not design experiments to disprove them. Not unlike for the war against terrorism, well-meaning people can take the same data and come to completely different conclusions.

CONCLUSION

The subject of clinical trials is vast. I have attempted here to provide a little history to help the general population understand the ambiguities, the time requirements and the cost. A trial is just that. It is taking a chance, not unlike playing a football game, investing in the stock market, or predicting the weather. We try to manage and reduce risk, but it is fair to say that we will never be able to eliminate it.

We want drugs that are safe, effective and cheap, but we can have only two of these in the early years of a newly-invented medicine. Eventually, we can have all three, but only after those who have accepted the risk of invention have seen a return on their effort. This includes all who invest in life science companies. Ultimately, free market capitalism drives cost down, just as we've seen for cellular telephones and the like. The generic drug industry works well, but invents little. To continue what Lind, Jenner, Ehrlich and colleagues started, we must continue to invest.

Glossary

(You will find a better glossary at www.centerwatch.com.)

Abbreviated New Drug Application (ANDA)

This filing with the FDA saves a generic company the better part of a decade and $1billion, a very sweet deal for the company, for patients and for Wal-Mart. This reflects the original concept of a patent – sharing art for a period of exclusivity, but not forever. While there are technical challenges with getting an ANDA approved, including demonstrating bioequivalence (see below), the effectiveness and safety issues surrounding innovation are not among them.

Adaptive Clinical Trial

A trial design whereby the data is analyzed along the way and decisions are made to modify the trial protocol going forward. Such a decision may include stopping the trial or changing its design to improve chances of a beneficial result. There has been much discussion on the topic and the FDA is to issue more definitive guidelines soon (2007). Adaptive design may allow for a continuous process rather than a series of trials with decision making in handing off from one to the next that takes much time. There are many logistical details to consider.

Adverse Events (AE)

Foul balls, strike outs, interceptions and stock market crashes, observations of undesired effects during a clinical trial or after a therapy is approved. There are many possibilities, but common among them would be nausea, dizziness, muscle aches, sleepiness, cardiac abnormalities, dry mouth, anxiety, headache, etc. You will see these mentioned on the "product insert" (pharma industry jargon) provided with every prescription.

The Body Hunters: How the Drug Industry Tests Its Products on the World's Poorest Patients by Sonia Shah (New Press, New York, 2006, 233 pp). The field of investigative journalism and its influence on drug policy goes all the way back to Upton Sinclair's book, *The Jungle*, a stimulus for founding the FDA in 1906. Very recently we've had *The Truth About Drug Companies: How They Deceive Us and What to Do About It*, by Marian Angell (Random House, 2004). In fact, there has been a series of "gotcha" books exposing the industry as evil incarnate. This latest book from Shah focuses on clinical trials in underdeveloped countries, and especially the notion of placebo-controlled trials that deny subjects viable therapy. Is a 50% chance of getting treatment better than a 100% chance of getting no treatment? Or is there an ethical obligation to treat everyone who participates with something, no matter what the cost? The latter can drive up the number of subjects required to the point where the trial becomes unwieldy in an underdeveloped country and thus might well never happen.

The books by Shah and Angell are annoying, but every pharmaceutical executive should read them. They can't help but invoke discomfort, and even anger. It's important to understand the widely-held point of view that greed drives all commercial decisions. My own perspective is that profit enables progress, just as war does. Pragmatists understand that reality is uncomfortable but they can deal with it. Idealists wish reality would go away and there would be no compromises among innovation risk, treating the sick, and rewarding investment. Meanwhile, there is no alternative.

When you read books purporting to expose the pharmaceutical industry, you will likely be outraged by the revelation of conflicts of interest. This is a pet peeve of mine. Our society is based on a commonality of interest. In free market capitalism, it's fair to say that if there is no conflict, there is no interest. If there is no interest, there is no progress. Doctors get paid to treat disease. Dentists get paid to fix your teeth. You pay them for what they propose doing to you. I suspect someone pays you for doing something for them as well. Is it a conflict of interest for a company to profit from developing and selling a drug? Sure. It's also an alignment of interest with those needing a cure. Would we pursue much pharmaceutical research if there were no profit? Would it all work better if rules were set to limit this profit? Could you buy a decent car in China before the government stepped out of the way? No, you were not allowed to own or even drive a car as an individual in 1980.

Free enterprise has its excesses, and there are plenty in pharma, but they don't last long because consumers and investors get angry and competitors get busy. This provides for a correction, which is often painful. Pharma is going through this now. They know the excesses of the 90s are over, generics are here, headcounts must come down, and efficiency must go up. They are kicking and screaming just as have sectors in automobiles, telephones, personal computers and others that had a sweet run. In the end, the system corrects and consumers win as competitors fight for advantage, often over a decade or so.

Marcia Angell seems especially disconnected from how markets work. (Apparently this was not covered in her medical school.) Her approach of price controls, limits on patents and an even tougher FDA are pretty well guaranteed to stifle innovation and leave the generics industry with nothing new to do a decade from now. Her book is helpful in awaking the industry to better behavior, but they will fix things best by fighting it out, not by following new rules of engagement. To counter Marcia Angell, M.D., I propose government price controls on visits to a physician with a limit of $20 for the first five minutes and $1/minute after that. I will discuss this with my doctor at my next visit.

Bayesian Statistics
Rev. Thomas Bayes died in 1761. Bayes' theorem was published in 1763 and relates to making logical inferences from probabilities. (Apparently back then it was considered sport to play with math between biblical studies because the World Wide Web had not yet been woven.) When you see words like these, think statistics and run and hide! The famous mathematician Laplace published a Philosophical Essay on Probabilities in 1814 in which he endorsed and explained Bayes' theorem, but not well enough for me to understand it 200 years later. If you need statistics, it means something isn't working well and we are not seeing the obvious cures of Edward Jenner, Paul Ehrlich or Gerhard Domagk. Today's diseases are tougher.

Bioequivalence (BE)
This term is used to compare two different formulations (for example, a tablet and a capsule). The idea here is to demonstrate that either formulation will result in a circulatory drug concentration that is statistically the same, and thus equally effective. BE trials commonly compare a generic formulation with that from the innovator company whose patent is about to expire, or already has done so. Profits then also can expire.

Canada
The place where Vioxx was discovered.

Cross-Over Design
This is not a fashion for cross-dressers, but a clinical trial where the subjects take one treatment and following a "wash-out" period, take another. The comparison can be between a drug and a placebo, between two different drugs, or between two doses of the same drug. Such a scheme would be used in a bioequivalence (BE) trial, for example.

Data and Safety Monitoring Board (DSMB)
An independent board of clinicians and statisticians who review data at specified intervals as a trial (usually a longer-term trial) proceeds. The trial sponsor does not participate in these data review sessions.

Double-Blind
Once is bad enough. In a double-blind study, neither the study subjects (a.k.a. patients) nor the medical personnel know which treatment the subject receives. When a study is "unblinded" it is like the masks coming off at a costume ball.

Exclusion Criteria
Originally used to deny women and other slaves the right to vote. In a clinical trial, there can be a number of exclusion criteria, often to exclude co-morbidities (simultaneous illnesses) which will complicate interpretation of the data.

Food-Effect Studies
This is not about weight gain and Type II diabetes. The oral bioavailability (BA) of a drug may well depend on whether it is dosed on an empty or full stomach/digestive tract. BA is a polite way of saying the drug got into circulation and wasn't peed or pooped away. For example, a comparison of dosing after a high-fat breakfast with dosing following an overnight fast provides useful information. There are specific interactions that can also occur with specific diets; for example, grapefruit juice is a common concern.

Health Insurance Portability and Accountability Act (HIPPA)
PUBLIC LAW 104-191, AUG. 21, 1996. Amends the Internal Revenue Code of 1986 to improve portability and continuity of health insurance coverage in the group and individual markets and to combat waste, fraud, and abuse in health insurance and health care delivery, to promote the use of medical savings accounts, to improve access to long-term care services and coverage, to simplify the administration of health insurance, and for other purposes as well. This makes uninteresting reading, plus it makes it very difficult to share medical records for research purposes, an unintended consequence.

Inclusion Criteria
To be accepted, you must be not too young, not too old, not too fat, not too thin, not too sick, but just right.

Institutional Review Board (IRB)
An independent group of professionals who review and approve the trial protocol for safety and soundness with respect to FDA regulations. They also review informed consent forms and any inducements to attract participants (e.g., advertisements).

Maximum Tolerated Dose (MTD)
How high can you go before adverse events become evident? Ideally, the dose to be used for effective therapy will be much lower.

Meta Analysis
Meta meaning later in time, at a later stage of development (e.g. metamorphosis). Here the term refers to using a series of randomized trials (for example, from existing literature) to develop a summary conclusion. Trials done at different times and places often come to somewhat different conclusions. Putting it all together, so to speak, presumably can help. There always remains the issue that a single physician with a single patient may not really fit any particular average conclusion from a group of studies or a group of patients. Lies, damned lies and statistics.

Multiple Rising Dose (MRD) or Multiple Ascending Dose (MAD)
This is similar to SRD and normally involves a randomized, double-blind, placebo-controlled protocol. The dose is administered more than once on a tightly defined schedule.

Non-Inferiority Trial
A double negative! A trial designed to guarantee that a new therapy is not worse than the standard therapy.
This may not instill a lot of confidence in the expenditure of R/D dollars. Such trials avoid use of a placebo (an advantage to subjects), but often require more subjects and a longer time to achieve statistical power.

Open-Label Study
All parties are informed of the drug and dose being administered. In an open-label study, none of the participants

are given placebos. These are usually conducted with Phase I and II studies.

Phase 0 Clinical Trial
A first-time-in-human trial in which the dose is far below that at which any therapeutic benefit or acute toxicology can be expected. The purpose and benefit of such a trial is somewhat controversial, although the general idea is to track pharmacokinetics before proceeding to a more conventional Phase I trial.

Placebo Controlled
Placebo is not a drill instructor for the Spanish Army. In this case the control or comparator group is treated with a dosage ("sugar pill" in the vernacular) known to be safe and totally ineffective. For a variety of reasons, "mind over matter" (also known as "the power of positive thinking") being one, placebos can be fabulously effective. On the other hand, when known therapy is available, it is not regarded as ethical to treat anyone with a medicine thought to be ineffective, and thus the comparator group is treated with known standard therapy.

Protocol
A fancy word for a detailed plan. What is to be done and for how long? Why is it to be done? How is it to be done? What's for breakfast?

Single Rising Dose (SRD) or Single Ascending Dose (SAD)
Small groups of subjects are given a single dose with each group receiving a larger dose in sequence. Results are reviewed before each subsequent group is studied.

Stopping Rules
Rules defined in a trial protocol designed to protect subjects from unsafe drugs or to speed more general use of an effective medicine. The Data and Safety Monitoring Board (DSMB) reviews results during the course of a trial and may invoke a stopping rule (normally for reasons of safety).

Subject
You! The participant. The volunteer.

Superiority Trial
A trial designed to show a new therapy is superior to existing therapy, avoiding the ethical dilemma of using a placebo. Only a statistician can explain to us how this differs from a non-inferiority trial (see above). Some old-timers (primarily physical scientists) will say if you need statistics to come to a conclusion, the experiment is not working. Isaac Newton did not develop laws that explain biology.

Vulnerable Subjects
Clinical trial participants who cannot give informed consent because of limited autonomy (e.g., children, the mentally ill, prisoners and those severely injured before they qualify for inclusion). Other subjects may be unduly influenced to participate (e.g., students, subordinates, employees and desperate patients). Economic rewards are appropriate for participation and include free medical exams, treatment and cash incentives. Balancing these with the risks of participation is always ambiguous.