4 WAYS TO FIX THE CLINICAL TRIAL

Clinical trials are crumbling under modern economic and scientific pressures. Nature *looks at ways they might be saved.*

BY HEIDI LEDFORD

Developing a drug is a costly gamble. Getting one to market takes, on average, more than ten years and a billion dollars. About 85% of therapies fail in early clinical trials. And of those that survive through to phase III, generally the last step before regulatory approval, only half will actually be approved.

Although a promising compound can fail for many reasons, from safety concerns to corporate decisions, many say that a significant number of good drugs are being lost to outdated and impractical clinical-trial designs (see 'The clinical-trial cliff'). The drugs may work, says Lillian Siu, an oncologist at Princess Margaret Hospital in Toronto, Canada, "we just don't know how to test them appropriately."

Solving the problem may require fundamental changes to the clinical-trial system to make it faster, cheaper, more adaptable and more in tune with modern molecular medicine. The old paradigm, established in the 1960s, was based on single trials, carried out at single sites, and designed to answer a single question, says Rachel Sherman, associate director for medical policy at the Center for Drug Evaluation and Research at the US Food and Drug Administration (FDA) in Bethesda, Maryland. "But that's not the world we're living in now."

Today, the world is more risk-averse, and demands larger trials to pinpoint safety concerns. Compounds that confer only small benefits when compared with existing drugs require large sample sizes for the results to be statistically significant. As a result, trials have become bigger, and often occur at

multiple sites, even in multiple countries, and can involve thousands of personnel.

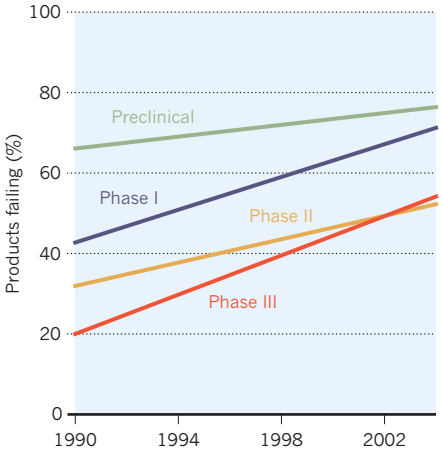
The long-heralded era of personalized medicine — tailoring treatments or combinations of treatments to a specific patient — adds its own complications. Such an approach has the potential to lower the failure rates of investigational drugs by testing them only in the individuals most likely to benefit. But research teams struggle to identify biological markers that can be used to stratify patients by the characteristics of their disease, and when they do, diseases can get splintered into rare subtypes that each affect just a few individuals. This means that researchers must screen a much larger pool of potential participants.

Some researchers are working to improve the fortunes of potential therapeutics, however. Here are four ways that they have come up with to give clinical trials a better success rate.

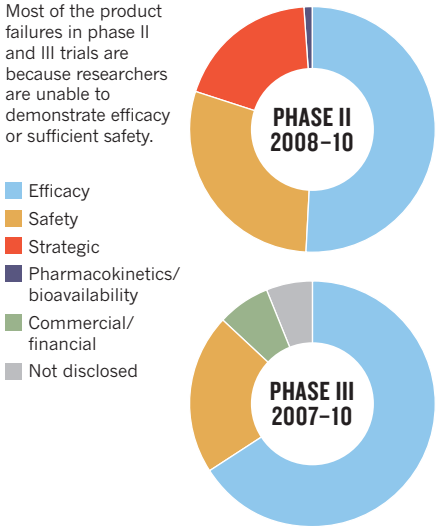
THE CLINICAL-TRIAL CLIFF

Drug companies are removing more compounds from the pipeline at all levels of testing than ever before.

For projects started between 1990 and 2004, the United States, Europe and Japan have seen sharp rises in the attrition of drugs tested in trials.



Most of the product failures in phase II and III trials are because researchers are unable to demonstrate efficacy or sufficient safety.



RECRUIT EARLY

Patient recruitment has been a major stumbling block. At least 90% of trials are extended by at least 6 weeks because investigators fail to enrol patients on schedule. Only about one-third of the sites engaged in any multicentre study ever manage to enrol the requisite number, says Kenneth Getz, an expert on clinical research at the Tufts Center for the Study of Drug Development in Boston, Massachusetts. The result: longer, more expensive trials — some of which may never be completed.

Personalized medicine, which has moved apace in cancer research and development, exacerbates the recruitment problem. George Sledge, an oncologist at Indiana University in Indianapolis, offers the example of a class of drug that inhibits enzymes called kinases. Imagine a trial that targets two kinases, one of which is mutated in 25% of patients, and the other of which is mutated in 8%. "You'd have to screen about 50 patients to find one eligible for the trial," he says. For more complex combinations and more diverse patient pools, the problem "gets to be virtually insoluble", he says.

Researchers and patient advocates are trying to make it easier to find eligible volunteers. They are taking a page from organizations such as the Alpha-1 Foundation in Miami, Florida, which has created a registry of patients with alpha-1 antitrypsin deficiency, a disorder that makes them particularly susceptible to lung and liver diseases, who are willing to be contacted about clinical trials.

The Moffitt Cancer Center in Tampa, Florida, for example, runs a Total Cancer Care programme that unites 18 hospitals, compiling medical history, tissue samples and genetic information about each patient's tumour. Samples are all stored for future analysis, and patients can consent to doctors contacting them about trials. A similar union of four institutions is in the works in the Netherlands, says Jan Schellens, an oncologist and pharmacologist at the Netherlands Cancer Institute in Amsterdam.

Negotiating agreements across institutions can be tricky. "Each brings its own values, preferences and interpretation of the privacy laws to the table," says Walter Kernan, a neurologist at Yale University in New Haven, Connecticut.

"To set up a system in which a hospital provides investigators at another institution with names of patients and diagnoses requires enormous trust."

Several groups that have been talking about forming networks are likely to face technical barriers. They need to develop appropriate patient-consent forms, unified databases and ultra-secure networks to connect hospitals. "Many of these groups don't have anywhere near the information-technology networks you'd need to carry this off," says Sledge. But that doesn't mean it won't happen, he adds. "It's the wave of the future, but it's not going to be simple."

SKIP ANIMALS

In 2009, researchers at the National Cancer Institute (NCI) in Bethesda faced a dilemma. They had evidence that blocking a protein called AKT, involved in cell death and proliferation, could stave off cancer, but initial animal studies on a compound that blocked the protein suggested that the drug was poorly absorbed by the human body. So researchers developed five formulations of the drug. The question was, should they test each one in animals, or could they skip ahead and evaluate them in humans?

In 2006, the FDA and the European Medicines Agency (EMA) introduced guidelines for testing very small 'microdoses' of drugs in humans. These are concentrations less than a one-hundredth of the therapeutic dose. Because the concentrations are so low, the drugs can be tested in a small number of patients without the level of safety data normally required before a phase I study. These early tests, dubbed 'phase 0' studies, would show, for instance, how the drug is distributed and broken down in the body, and whether it hits the right molecular target.

Paul Limburg, a gastroenterologist at the Mayo Clinic in Rochester, Minnesota, decided to launch a phase 0 study of the new AKT drug formulations. The results, published in March, allowed the team to pick the one absorbed best by the body for use in future trials (J. M. Reid *et al. Cancer Prev. Res.* **4,** 347–353; 2011).

Proponents of phase 0 testing argue that it makes sense to get human data quickly. About one-quarter of the molecules entering clinical trials fail because of "poor pharmacology", says Schellens. The drug may not be readily absorbed, for example, or may not reach its target organ. With a simple test in humans, he says, "you could kill that drug much earlier, before you have invested so much time and money".

But Razelle Kurzrock at the MD Anderson Cancer Center in Houston, Texas, is concerned that developers will kill promising drugs in response to negative microdose data, even though the drug may work at higher, therapeutic concentrations. To test this hypothesis, she and her colleagues are conducting phase 0 trials with FDA-approved drugs to find out whether any would have failed at that stage.

And phase 0 trials may be tiny, but they are not easy. They require a test sensitive enough to detect the minute quantities of the drug in the body — and possibly also ways to track its mechanism of action. For veliparib, a ▶

potential anti-cancer drug, Abbott Laboratories, headquartered in Abbott Park, Illinois, started developing assays that were robust and sensitive enough to detect tiny concentrations of the drug more than a year before its researchers embarked on a phase 0 trial, says James Doroshow, the NCI oncologist who led the trial.

Few, says Schellens, plan so far ahead. "Often when people start thinking about the phase 0 trial in the drug development process, they are too late."

USE MODELS

Although phase 0 trials could help to wean researchers off pharmacology studies in animals, moves are also afoot to bring mouse experiments closer to the clinic.

The problem with most of today's animal studies, says Eric Holland, a neurosurgeon at the Memorial Sloan-Kettering Cancer Center in New York, is that they typically focus on safety rather than efficacy. And they rarely predict exactly what will happen in the clinic, because the doses, formulations and schedules of medication differ from those given to the animals. A person with prostate cancer, for example, does not usually take an experimental medication until the standard hormone therapy has failed. But the mice that experimental drug was tested on are unlikely to have received the same treatment.

Pier Paolo Pandolfi, a cancer researcher at Harvard Medical School in Boston, has therefore pioneered a technique called the 'co-clinical trial', in which mice with similar disease characteristics are treated in a similar way to the humans. Holland recently used the approach to test combinations of drugs that target AKT and another protein, called mTOR (K. L. Pitter *et al. PLoS ONE* **6,** e14545; 2011). The mouse trial allowed the researchers to try more concentrations than the human trial, and suggested new ways of screening patients for inclusion in future clinical trials. "The more complicated the trial, the more likely it is that the co-clinical strategy would be beneficial," Holland says.

In 2009, the NCI invested US$4.2 million in Pandolfi's co-clinical trials in prostate and lung cancer. In them, mice receive the same therapies as people do before the start of experimental treatments. At The Jackson Laboratory, based in Bar Harbor, Maine, which has a large personalized medicine programme, researchers graft tumour cells taken from patients into mice. These mice can then be given the same treatment as the patient, so that researchers can track how the tumour cells respond, and use this information to tailor future treatment for the patient.

ALTER COURSE

Perhaps nowhere in science is ignorance prized as highly as in clinical trials. To keep expectations or biases from inadvertently influencing the results, patients and investigators are often kept in the dark about who is receiving what treatment until the end of the study. At best, an external committee may take a secret peek at the results mid-trial to make sure it is safe for the experiment to continue.

But looking just once at the data is "like driving home from work and only opening your eyes once to see where you're going", says Donald Berry, a statistician at the MD Anderson Cancer Center.

Berry specializes in designing 'adaptive' trials, which can change course as the data roll in. If one treatment regimen seems to be more successful, for example, researchers might increase the proportion of participants that should receive that treatment. These trials can also be used to identify biological markers, such as mutations or altered metabolite levels, associated with the success or failure of a given regimen.

For example, before women enrol in an ongoing adaptive trial called I-SPY2, run by Berry and Laura Esserman, an oncologist at the University of California, San Francisco, their breast-cancer tumours are biopsied and tested for genetic markers. The genetic make-up of their tumours determines whether they are eligible to enter the trial, and which group of treatments they should be randomized to. But because the results are reanalysed each time a woman completes her treatment, the participants are more likely to receive a treatment that has worked in people with genetically similar tumours. If a treatment does not perform well in any patients, it is cut from the programme; other treatments can then be added to the mix.

AS THE MOLECULAR ERA ARRIVES, ADAPTIVE TRIALS WILL BECOME MORE AND MORE RELEVANT.

The FDA and the EMA have encouraged drug developers to embrace these designs. In addition to high-profile trials such as I-SPY2, Berry says that he has designed trials running the whole gamut of disease, from diabetes to pandemic flu. "Virtually every pharma company is doing this," he says. But Getz disagrees and says that he's seen a more muted response to adaptive trials. "Our clinical-trial protocols have become too complex across the board," says Getz. "And adaptive designs add to the logistical complexity."

One issue is statistical: the more tests on the data a researcher conducts, the more likely it is that they will introduce false positive results. Scott Evans, a biostatistician at the Harvard School of Public Health in Boston, is more concerned about bias, however. Even if it is an independent panel that views the data and adapts the trial, it is often impossible to hide a change in protocol from everyone. "Any in-flight adjustment you make in a clinical trial is potentially observable," he says. "Now you've created the potential for an operational bias."

"There has been a lot of controversy about adaptive trials," Siu says. "But as the molecular era arrives, they will become more and more relevant."

TEAR DOWN OR TWEAK?

While researchers dream up new, better ways to design clinical trials, many involved acknowledge that the changes with the biggest impact will probably be more bureaucratic than conceptual.

Simply standardizing the forms used to record clinical-trial data would reduce costs and cut down on record-keeping errors and omissions. The NCI is now rolling out a data-management system that will standardize data entry across all 2,000 sites that conduct NCI-sponsored trials, says Doroshow. The FDA is also looking at ways to cut down on reporting requirements and paperwork, so that investigators can submit summaries of case reports rather than each individual document.

Trials that involve multiple sites also have to get approval from each institutions' review committee, referred to as an institutional review board. This can take months or even years.

To adapt to the multicentre climate, the US Office for Human Research Protections in Rockville, Maryland, which oversees human studies funded by the US National Institutes of Health, has proposed changes to its guidelines that would require designation of a single review board for each project. However, individual research centres may be reluctant to loosen their hold on the reins.

The clinical-trial system may be outdated, but at least it is not inflexible. Most radical designs have probably been tried in some capacity. Getting rid of control groups? It happens in rare-disease trials. Blending phases? Some trials are already starting to do this. Still, even small tweaks require a leap of faith when they are being made to a complex system with such high stakes — the protection of human health.

The way that clinical trials are designed and run may need to be revolutionized, but "there's not going to be a single solution because it's a multifactorial process," says Richard Schilsky, an oncologist at the University of Chicago, Illinois. "Everybody who is a stakeholder in the clinical-trial process has to contribute to the solutions." ■

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