

Overhauling clinical trials

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Designing clinical trials that adapt midstream is billed as a cure for drug development blues, one that can save time, money and improve patients' lives. Are these new designs safe and effective or an expensive gimmick?

Wearied of rooting around for marginal improvements such as rapid patient enrollment and electronic case report forms, drug industry executives, government regulators and academic scholars alike admit that the gold standard for testing drugs—randomized controlled clinical trials—has lost its luster, and restoring it needs more than a polish. Time consuming, expensive and prone to failure, current methods for clinical development are ripe for reconstruction.

New clinical trial techniques are designed to adjust the course of a clinical trial as data accrues. Most of the major drug companies have published articles on designing such trials, often referred to as 'flexible' or 'adaptive'. Ken Getz, senior research fellow of the Tufts Center for the Study of Drug Development (Boston) says drug companies are not just applying adaptive designs to individual projects but moving to spread them across their portfolios. Donald Berry has scheduled over 100 such cancer trials at the M.D. Anderson Cancer Center (Houston), where he is chair of biostatistics.

Regulators are getting involved as well. The European Medicines Agency (EMA) issued a reflection paper, loaded with caveats, on confirmatory trials with flexible designs implying that it would consider companies' arguments for their use¹. The US Food and Drug Administration (FDA) telegraphed its support for new clinical trial methodologies by issuing draft guidelines for medical devices. Late last year, the agency helped organize a closed session of industry biostatisticians and FDA officials to tackle ways of streamlining drug trials, with a focus on adaptive designs.

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Luck of the draw. In one design, patients receive treatments depending on what ball is drawn from an urn. When a patient's treatment is successful, a corresponding ball is added to the urn, boosting the chance that subsequent patients will receive that treatment

Enthusiasm was described as overwhelming, with over 300 people attending and more clamoring, unsuccessfully, for invitations.

One agenda item: figuring out what the term 'adaptive trial' really means. "It isn't very well defined," says Robert Temple, director of medical policy at the FDA. That only adds to the controversy, according to Michael Krams, vice president of adaptive designs at Wyeth in Collegeville, Pennsylvania. "This term is just a lightning rod," he says. "We've put together a totally different way of clinical trial planning."

Although describing streamlined solutions can be fuzzy, the target is clear. Cheaper, faster trials may help to reduce the stratospheric

cost of drug development and quell ethical problems in assigning patients randomly to treatments. By some estimates, streamlining late-stage studies could reduce the numbers of enrolled subjects by half and the time to market by months, theoretically saving hundreds of millions of dollars and getting medicines to patients faster. But others argue that adaptive designs hold high hidden costs and that modifying the conditions of an ongoing trial compromises its ability to answer an experimental question.

Designer trials

In randomized controlled trials, used for more than half a century, biostatisticians restate hoped-for answers to clinical questions as testable hypotheses. Using a set of assumptions based on animal studies and previous human trials, they compute the sample size necessary for testing and predict which treatment differences are likely to be clinically meaningful. Randomized controlled trials typically use frequentist statistics, a classical interpretation of probability. *P*-values and confidence intervals both ascertain how likely an effect is to occur if the experiment is repeated and indicate whether observations might occur by chance.

Critics say the lock-step routine of a randomized controlled trial is its undoing. Every trial is conducted as an experiment, and traditional rules say 'no meddling' until the experiment runs to completion. When a conventional trial ends in failure, many blame the trial design. Researchers muse that different conditions—a longer time frame, a different route of administration, another subpopulation—could have shown the drug's true efficacy. "When they started with randomized trials, everyone thought you test one hypothesis and come up with an answer, but you don't," says Brian Schwartz, chief medical officer with Ziopharm (Charlestown, MA, USA), an oncology biotech, who helped design the trials that sampled

Box 1 Adaptive trials: classification and terminology⁷

Several terms are used to describe the different types of adaptive trials and the strategies used in them. Some of these are defined below:

Changing allocation rules. New subjects are assigned to available treatments based on accruing data. The success of one treatment results in the next patient's assignment to that same treatment. Most common is the randomized play-the-winner rule (also called response-adaptive trials). A Bayesian response-adaptive strategy alters allocation based on hunches about the 'best' treatments. Allocation changes include dropping or adding treatment arms.

Changing sampling rules. Adjusting the number of subjects sampled at the next stage of the trial. For example, first the data are unblinded and analyzed. Then the sample size is adjusted so that enough patients are enrolled to demonstrate a prespecified effect.

Special stopping rules. A central feature of traditional trials, these preset rules protect patients by stopping trials that demonstrate benefit, harm or futility by showing that an experimental treatment is better, worse or no better than a control. Stopping rules may be Bayesian, based on the possible consequences of continuing the study.

Changing decision rules. Changing the test statistics, the endpoints, the hypothesis (e.g., switching from a superiority to a noninferiority trial), or the patient population.

Sequential designs. During phase 3 trials, an interim test statistic measures the advantage of a treatment compared to the control. If it is 'within bounds', the trial proceeds; if out of bounds, the trial stops. Statistics can be applied after every patient's result (full sequential), or after groups of results (group sequential).

Flexible designs. Mid-trial alterations, such as combining *P* values from two independent samples regardless if they are based on the same clinical endpoint, or building trials with variable numbers of stages. These decisions may or may not be fixed a priori, but experts suggest that contemplated alterations are set beforehand.

Adaptive dose finding. Preliminary estimates of clinical benefit among a range of doses determine the best dose. Then, a new cohort of patients is assigned to that dose. This dose-to-dose strategy satisfies collective ethics—finding a dose that is best for future patients. Continual reassessment of a dose escalation study within a cohort of patients can also satisfy individual ethics—in this case, the next patient is allocated to what appears to be the best dose.

Seamless trials. Phase 1 determines a dose that is considered a safe maximum tolerated dose (MTD) and phase 2 explores doses that are efficacious. In certain cases trials can be designed to answer both questions simultaneously. Similarly, a phase 2b selection of the best treatment can be combined with phase 3 confirmation of that treatment against a control, either placebo or standard.

Rosenberger, chair of applied and engineering statistics at George Mason University in Fairfax, Virginia, says "in my area, it means response-adaptive designs, when we look at the treatment outcomes before randomly assigning the next patient coming into the trial." "Adaptive trials are redesign on horseback," quips Phillip Lavori, head of health research and policy at Stanford University (Stanford, CA, USA). Put another way, adaptive trials bet on the lead horse while the race is being run.

Scott Emerson, a biostatistician at the University of Washington, Seattle, wonders about studies that change how patients are sampled after observing an estimate of the treatment effect. He worries these midcourse changes are equivalent to "changing the questions along the way, rather than asking the questions first and then letting the data answer them." Emerson argues that designing trials with prearranged rules to stop the study because of harm, benefit or futility is the best way to preserve the classical approaches of hypothesis testing².

But adaptive trials are not really about improvisation; trial designs map out multiple possible scenarios and fashion protocols for each. Even aggressive advocates insist that responses to observations be planned in advance. Once the trial starts, the variables set to trigger decision points can't change or the integrity of the trial will be destroyed. "Adaptive design must be rigorous," says Peter Ho, vice president of oncology and discovery medicine at GlaxoSmithKline (Research Triangle Park, NC, USA). He says a perfectly designed trial wouldn't need to adapt. "Fundamentally, all trials can be done adaptively," says Jerald Schindler, president of the Pharmaceutical Research Division at Cytel (Cambridge, MA, USA), which helps companies simulate and design trials (Table 1). "It's not whether it's adaptive or not, but how many adaptations could occur in the course of the trial."

Advocating adaptivity

There are two major reasons why the drug industry likes flexible designs. First, these trials are widely believed to be shorter, smaller and cheaper than conventional clinical studies. Individual phases can be merged, too, shortening or eliminating delays between trials. Midstream alterations might include adjusting the sample size based on new information (collapsing one arm or repowering, that is, adding more patients to another), changing a dose or schedule of treatments, refining the randomization scheme, switching from one statistical test to another, substituting a new clinical endpoint or modifying the original hypothesis. The second advantage is that such

Bayer's small molecule Nexavar (sorafenib) in multiple tumor types before settling on kidney cancer.

Adaptive trials check data during the trial and use accumulating information to alter the direction of the study. Thus, say advocates, adaptive trials can sample more conditions and give drugs a better chance to show their worth. A conventional randomized controlled trial that hit on optimal conditions would take less time and require fewer patients, but with so many drugs failing clinical trials, adaptive designs are often seen as the better bet for steering patients toward effective treatments and companies toward better investments in drug development.

As with most things that are presented as new and improved, adaptive trials and their kin have been around for a while. They boast connections to Thomas Bayes, a British 18th century theologian and mathematician. Bayesian

methods allow nonfrequentist interpretations of probability. As new information accrues, it is used to update and refine the original hypothesis. Filters that catch junk e-mail show Bayes' theorem at work: when users identify spam, the reference set defining spam is updated, thereby constructing a new filter. Biostatisticians using Bayesian approaches examine data throughout a clinical trial. Based on their observations, these trials can change the probabilities so that subjects will receive what appears to be a superior treatment. Trial designers already agree on essential elements that deviate from randomized controlled trial designs, naming them according to how the trial might change: 'response-adaptive design', 'sequential design' and 'adaptive dose-finding' (Box 1).

Responses to data accrual are preplanned. "You build in actions that depend on interim observations and modify the trial as you go," explains M.D. Anderson's Berry. William

Table 1 Selected adaptive trial planning companies

Company (founded)	Financing	Selected software
Pharmaceutical Research Division, Cytel Statistical Software and Services (division 2005; company 1987) (Cambridge, MA, USA) http://www.cytel.com/	Private	East software for designing, monitoring and simulating trials. Also FlexRandomizer, StatXact and LogXact.
HealthDecisions (1989) (Chapel Hill, NC, USA) http://www.healthdec.com/	Private	Technology to capture data quickly for early decisions. Includes SmartMonitoring, web applications, Smart Pen.
Pharsight (1995) (Mountain View, CA, USA) http://www.pharsight.com	OTC BB: PHST.OB Market cap: \$31 million	Trial Simulator for designing and simulating trials. Also, WinNonlin.
Quintiles Strategic Biostatistics Services (division 2006; company 1982) (Durham, NC, USA) http://www.quintiles.com/	Private	None described.
Tessella, Inc. (adaptive trial division 1998; company 1980) (Abingdon, UK) http://www.tessella.com/	Private	Clinical trial simulators; statistical models include bivariate continuous reassessment method (bCRM) and Toxfinder.

Sources: Company websites, Yahoo Finance.

trials can provide better medical care by funneling patients into arms that show promise and moving others out of treatment failures. M.D. Anderson's Berry, also an industry consultant, adds a third reason to adapt: fear. Drug companies reluctant to embrace the new methods may get left behind.

Supporters say adaptive trials have ethical benefits that traditional trials lack. Risks and benefits of randomized controlled trials are often measured against two standards of clinical ethics. The first—and most important—standard focuses on the physician's responsibilities to individual patients: do no harm and provide the best standard of care possible. The second set of standards includes ethical dimensions that affect society. Knowledge gained from clinical trials benefits science overall, and information about new treatments gleaned from one trial can be used to benefit other suffering and sick patients.

Clinical trials can pit individual and group ethics against each other. For example, the very act of randomization means that two patients with equal need may get unequal treatment. Also, a randomized controlled trial is predicated on genuine uncertainty: it is a rigorous way to answer a question about which drug is better. But clinicians often have strong hunches about the efficacy of new treatments. Though they may lack unbiased statistical evidence to support their view, they feel one approach is better than the other. Thus, submitting patients to large randomized trials seems unethical.

Flexible studies address some ethical sore points of traditional clinical trial design, especially those that involve risky human experimentation. Studies can be designed so that the fewest volunteers are needed to produce a statistically significant result, and that can benefit patients. Compared to traditional studies

exploring dose-response curves, for example, adaptive designs mean fewer patients are subjected to ineffective or toxic doses. "Usually you have to drive each arm of the study to completion, even at doses that aren't effective," explains GlaxoSmithKline's Ho. But adaptive trials study more-effective doses in more patients, allowing fine tuning. "Interim evaluations may reveal the low dose as ineffective, or a higher dose with toxic effects. You stop those arms, and add patients to the effective treatment—the new learnings benefit patients as the trial progresses."

The end result may be fewer total patients enrolled (and less total group risk) in a trial

that still shows a significant result. James Waun, vice chair of the Michigan State Medical Society (East Lansing, MI, USA) and head of its bioethics committee, says as long as trials are properly designed and independently monitored, flexible studies can benefit patients. "Moving subjects into effective treatments mirrors how doctors actually practice medicine," he says.

The downsides of new designs

But adaptive designs aren't necessarily more ethical (Box 2). Biostatisticians, physicians and ethicists worry about a number of potential pitfalls. Volunteers may wait to enroll, betting that latecomers are more likely to be assigned

Box 2 Gambling on ECMO

In the 1980s, neonatal experts at the University of Michigan Ann Arbor found they could save 70% of infants dying from severe respiratory failure with a treatment called extra corporeal membrane oxygenation (ECMO). Before the treatment could be adopted widely, however, it had to prove itself in a randomized trial⁸.

But how could pediatricians, especially those who regularly provide ECMO, agree to a classic RCT, where half the infants would get the standard treatment and surely die? A solution was proposed, one that adapted the randomization of the trial as it went along. An urn contained two balls, one labeled 'A' for the ECMO procedure and 'B' for conventional therapy. Each infant's treatment was determined by drawing a ball from the urn, which was then replaced. If the treatment worked, a ball representing that treatment was added to the urn, so that the next infant in the study was more likely to receive a treatment shown to be effective. The trial ended when ten balls of one type were added.

The first infant received ECMO and lived. The second did not, and died. The next ten drew 'A' and survived; ECMO was declared a winner and the trial stopped.

Did this adaptive design yield the best ethical result? Some say yes: a 50/50 randomization would have meant death for five infants, not one. But physicians have a duty to provide the most effective treatment for each patient, and those involved in the trial had already seen ECMO save lives. Critics said doctors should have referred the 'B' infants to hospitals known to practice ECMO or found collaborators at another hospital that did not use ECMO, even though that would have meant more infants died.

Though researchers are now more likely to use computers than urns to assign treatments randomly, the ethical questions are as complex as ever.

to effective treatments. Patients who enroll at the start of the trial might be different from or encounter different expectations than patients who enroll later, a bias that is hard to control.

The tension between personal and group ethics grows especially taut as clinicians gain information, such as new data; as enrollment changes, adding or subtracting treatment arms; and as endpoints are moved. The ethical principle of equipoise demands that real uncertainty exists about which treatment will benefit the subject most. Maintaining equipoise is tough enough for randomized controlled trials; it's even tougher for adaptive trials. Rather than suspending hunches and opinion in favor of the hard statistics of a blinded, placebo-controlled trial, doctors conducting adaptive studies are faced with a growing awareness of what might be working. Temptations to steer the neediest patients to those treatments will grow, too.

Prior knowledge about how these trials work begs a question at the heart of clinical ethics: what kind of informed consent is needed, and how best to communicate it? George Mason University's Rosenberger has authored a textbook on adaptive trials and writes about the ethics of alternate designs for phase 3 studies³. He wonders about revealing the fine points of a dosing trial. "In the informed consent process, do you say 'well, we will give you a very low dose that won't be very effective; or a higher dose that might make you sick: Which do you want?' Do we really want to put this decision into patients' hands?" he asks.

Another worry is that early signals that influenced patients' treatment assignments could turn out to be false. Trial planners have to contend with the fact that the most definitive results might come only after the decisions based on preliminary results have been made. For example, the first reading of tumor response will likely come from oncologists associated with the trial, whose interpretations tend to be more optimistic than those of the independent experts. "When you're using adaptive design, you have to consider that these data are not 100% like what you'd get later," says Mark Chang, a biostatistician at Millennium Pharmaceuticals (Cambridge, MA, USA).

Biostatisticians worry that changing the sampling plans after observing a treatment effect can introduce noise and errors into the analysis. There are efficiency penalties, too. If the clinical effect is smaller, or the placebo effect larger, than expected, more patients must be added to achieve statistical significance. Stanford's Lavori uses a drug trial for hypertension as an example. "The study design plans for a big blood pressure-lowering effect, say, one standard deviation. If you see half the effect—and want to continue the trial—you need to enroll

four times the patients to get a statistically positive result." In either case, the hoped-for savings from smaller trials could evaporate as studies adapt to gain statistical significance.

A researcher might plan to enroll 100 subjects, but halfway through, recruit more subjects in an attempt to achieve a significant result. Such contingencies should be anticipated and evaluated before a trial begins, says Cytel's Schindler. "You can simulate many things before you do the trial and make decisions. You can then compare a conventional trial to the adaptive designs," before actually enrolling any patients.

Oversight mechanisms will need adjustment, too. Independent data monitoring committees, or DMCs—boards made up of clinicians, biostatisticians and bioethicists—apply ethical standards, stopping the study if the data demand it. In traditional trials, the boards are privy to information that treating physicians shouldn't see. Adaptive designs with a cascade of complex rules that accompany them will regularly 'break the blind', meaning that DMCs will have to communicate some changes with those running the trial.

One way to get around revealing the results of an ongoing trial is to give DMCs more leeway. If the rule about changing a sample size is closely tied to a drug's effect, everyone will know how well the drug is doing. However, if the DMC is asked to adjust sample size to maintain an approximate level of statistical certainty, information can remain (somewhat) masked.

Under ideal scenarios, people running the trial won't even realize that a protocol has changed at all. But ideal scenarios happen by design. For example, Wyeth's Krams recommends that dose-finding studies manufacture the drug in pills or infusion packs in coded concentrations of 0 \times , 1 \times , 2 \times , 3 \times and 4 \times . That way, clinicians can adjust the dose of a drug eightfold while using only two packaging units of the study drug without knowing what, if any, change has been made.

Inevitably, though, clinicians will learn of some shifts in the trials they conduct. One researcher described a study that required patients to take over a dozen tablets at a time, "a breakfast of pills," as a study scanned for the most effective dose. Study sites might also be asked to change the timing or frequency of drug administration. And if a study homes in on a subpopulation, clinicians are unlikely to miss that their study patients have gone from all-comers to, say, nonsmoking Asian women.

Adapting business

Such changes have significant business implications. Even though drug companies can specify

what a DMC will monitor, companies can be reluctant to let independent DMCs decide whether to continue pouring resources into a drug that may work only for a small population or under inconvenient conditions. A separation between phase 2 and 3 trials, although time consuming and expensive, gives drug developers a chance to rethink before launching the next study. In a seamless mega-trial overseen by a DMC, corporate executives fret about loss of control.

ZioPharm's Schwartz says that most DMCs are given only enough data to determine whether a study crosses a safety or efficacy threshold, but handing more control over to DMCs could mean more informative trials. "The more data they see, the more they can help the trial," he says. Even if companies were willing to give up control, they might not be able to find statisticians ready to take it. "Most DMCs have experience to monitor the classical conventional trials but don't have experience for adaptive design," says Millennium's Chang. "They are sort of scared." The FDA's Temple sees identifying the responsible party for making adaptive decisions as a major issue, especially considering the conflicts of interest of safety committees embedded deep inside pharmaceutical companies. "You don't want a committee noodling around making changes," he says.

Designing in as many branch points as possible might seem unwieldy. Inputs from physicians, biostatisticians, pharmacologists, patient advocates and the company's marketing group must all be considered. Add to that calculations of sample distribution, false-positive rates, the amount of drug to supply and enrollment numbers. But the end result will be a study that runs smoothly. Before the trial starts, teams should reach a state where "everything is spelled out and everyone agrees," says Berry. "I say we ask the tough clinical questions up front, and let the company make the call. They have to work to set down the rules, but if they do a good job of it, the DMC becomes an automaton."

Negotiating logic

It's one thing to ponder how a theoretical trial could shift midcourse to veer away from ineffective treatments. It's quite another to put the resources in place to collect, interpret and act on data as it accumulates in an ongoing trial. Biostatisticians and clinicians say that adopting flexible designs will take work, and that companies must be prepared to pay for it. "The best investment of time is in early planning," says Krams, Berry who helped design one of the first large adaptive trials that was both deemed definitive and published in the literature,

Table 2 Selected EDC companies

Company	Products and services	Disclosed clients (partial lists)
MediData Solutions (New York)	Data capture and management software Rave; hosting, support and training services.	AstraZeneca, Bayer, Corus, Gilead, Infinity, Merck, Pfizer, Vertex.
Oracle (Redwood Shores, CA, USA)	eClinical suite consists of management, dictionary, hub and other packages.	Applied Biosystems, Boehringer Ingelheim, Dendreon, Icon, Novartis, Wyeth.
PhaseForward (Waltham, MA, USA)	Data capture and management, and safety-monitoring software.	AstraZeneca, Boston Scientific, Eli Lilly, FDA, GlaxoSmithKline, Merck.

Pfizer's ASTIN (Acute Stroke Therapy by Inhibition of Neutrophils)⁴. That study showed that an experimental stroke drug was ineffective in less time and with fewer patients than would have been necessary in a conventional trial.

Negotiations must occur across all the groups involved in running a trial, from patient enrollment, to information technology, to drug manufacture and distribution. Clinical trial sites must be careful not to enroll patients too quickly, or they may end up with patients they don't need. A laboratory that normally waits for blood samples from patients to accumulate and then runs them all in one batch may need to analyze samples as they come in instead, because trial organizers must see ongoing results to know how to adjust the trial.

Ideally, a signal can be measured soon after a patient is treated. When robust measures of efficacy are a long way off, like five-year survival in cancer patients, researchers must decide whether they can make decisions based on earlier, less certain measures, like one-year survival or tumor response. To some extent, uncertainty around biomarkers can be modeled into the statistics governing the trial. In some cases, adaptive trials can be designed to make decisions based on early endpoints and continue to collect later, more-certain endpoints.

Doing data digitally

Gathering data quickly is crucial for trials with flexible designs, and companies running adaptive trials will have to invest heavily in information technology. Optimistically, ~40% of all clinical trials use electronic data capture (EDC) software. Still, Ziopharm's Schwartz estimates that fewer than half of clinical trial investigators prefer the web-based systems that move data directly into a central database.

Traditionally, data from clinical trials trickle in as clerical workers transcribe information from paper-based forms filled out by clinicians. An EDC system can detect many discrepancies in real time, which can mean that data are ready for analysis more quickly, but resolving errors often requires people who understand the clinical trials and patients' charts. Study sites balk at hiring more-qualified people for

data entry, and clinicians who willingly fill out paper forms at the bedside may balk when asked to sit down in front of a computer.

Electronic data collection can be particularly difficult to coordinate across international study sites because electronic forms assume that all sites will record data in the same way. This is a problem when some sites record qualitative impressions of a patient's condition and others use more quantitative, standardized measures. Millennium's Chang recalls a situation where his company assumed it could get information through an EDC system, but ended up having to go back to the original paper case-report forms, causing unplanned delays. "You have to be very, very careful," he says. "You need to go to the site and really understand what the site can do."

Conversely, sponsors of adaptive trials can use EDC to make sure that sites are collecting data appropriately and quickly, says Paul Bleicher, founder of PhaseForward (Waltham, MA, USA), a company that sells and implements EDC software (Table 2). Instead of waiting for weeks to see how a trial site is doing, clinical trial monitors can check progress daily. Such monitoring can help predict when enough data have been collected to make a decision, and warn company executives or DMC members to schedule a meeting.

The ability to make good, frequent decisions quickly is one of the biggest stumbling blocks in adaptive designs. "What drug companies are struggling to do is to change their

decision-making from one that has been largely retrospective to something that is much more prospective," says Glen de Vries, chief technology officer at MediData, another EDC vendor. The time savings of collecting data electronically within a day or two of the patient visit is actually small compared with the delay caused when data from disparate sources must be brought together so that treatments can be matched with outcomes, and decisions made. Reconciling data this way requires the data managers and biostatisticians to work together so that no one glimpses unblinded data unless they are supposed to. If companies don't plan ahead, they won't be ready for data when the data are ready.

Delays in making and acting on decisions erode the advantages of adaptive designs, says Cytel's Schindler. "If you take several weeks to go through these steps, you've lost much of the opportunity to benefit from the change."

Nimble trials or nimble firms?

Ultimately, the power of adaptive designs to streamline clinical trials may depend as much on individual teams and companies as on the overall concept. "What we're really finding is there is no single technology or process improvement or technique that's driving speed," says Tufts' Getz.

Getz recently completed a study that looked at the development times for 104 approved drugs at 29 drug companies and found that the five fastest companies had clinical development times that were well over two years faster than the slowest companies⁵. They broke the analysis down by therapeutic areas and drugs' mechanisms of action and found that the fastest companies were consistently faster than their peers.

In fact, the fastest ten companies terminated 56% of their trials in phase 1 compared with 36% of the slowest ten companies (Fig. 1). For phase 2 trials, the numbers were roughly the inverse. Still, Getz is not convinced that the faster companies are actually gleaning more informa-

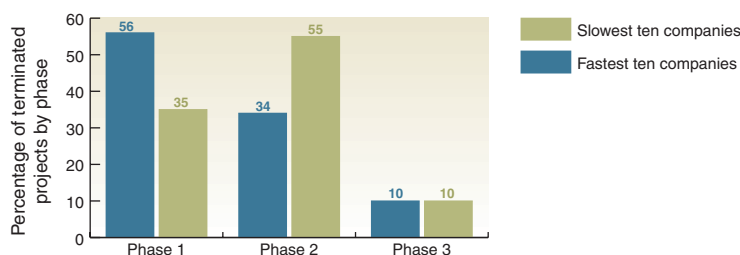


Figure 1 Percentage of terminated projects by phase (1994–2005). Terminating clinical trials early helps speed drug development times. Other factors include: collaborating actively with regulatory agencies, using electronic data management and higher levels of outsourcing. (Source: Tufts Center for the Study of Drug Development, Boston.)

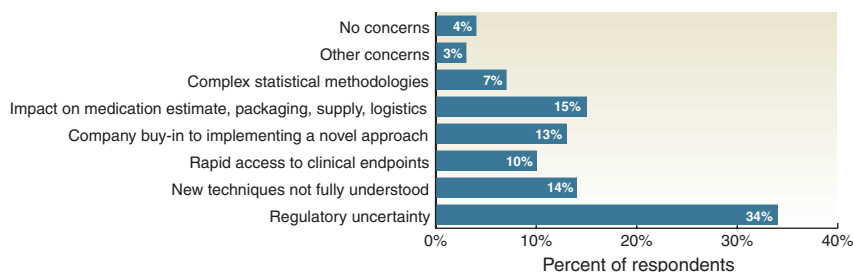


Figure 2 Perceived barriers to adaptive trials. According to a survey of companies, regulatory uncertainty represents the biggest barrier for the implementation of adaptive trials. Unfamiliarity with the methodology and logistical problems also weigh heavily. (Source: Cytel, Cambridge, MA, USA.)

tion from their phase 1 trials than the slower companies are. Instead, he believes, faster companies are better at acting on that information.

“The real skill these companies have is of making decisions quickly,” says Getz. The fastest companies weren’t any more likely to use EDC than the slower companies, for example, but slower companies’ piloting and use of the technologies were more compartmentalized, stuck within particular projects or therapeutic areas. “The fastest drug development teams seem to embrace these technologies and implement them more consistently across their portfolio.” They also tend to assign decision-making responsibilities to “the appropriate levels of authority.” Though individuals across the company may be asked for opinions, only a few make the decisions. This sidesteps the need for large groups to reach consensus.

Getz thinks that advances in information technology and statistics will have only marginal benefits for many companies. “Many of the improvements will only deliver higher levels of efficiency if you have the right mechanisms to adopt them, implement them and support them.” In other words, the power of adaptive designs and other techniques to streamline clinical trials may depend less on the skill of statisticians, and more on decisive management.

Of course, management has its reasons for being leery of adaptive designs (Fig 2). No company wants to complete a trial only to have regulators second-guess it. Plus, over a third of the companies worry about understanding and gaining support for new, complex methodologies. Nonetheless, adaptive techniques are rapidly penetrating early-stage trials, and regu-

lators are keen to learn how to weigh results for larger, later-stage ones.

The 1990s drug development mantra “fail early and fail often” may yield to a new, but familiar refrain: “adapt or die.” Richard Royall, an emeritus biostatistician at Johns Hopkins University (Baltimore), argues in his seminal 1991 paper on the ethics of clinical trials that the tyranny of mathematics shouldn’t overwhelm the medical community’s ethical obligations about what’s best for the patient⁶. Good advice for the next wave of clinical trials, whatever form they might take.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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