Reinventing clinical trials

Malorye Allison

As R&D costs spiral for drug developers, disruptive approaches to clinical trial design and management are gaining traction. Get ready for electronic data capture, precompetitive data sharing, virtual trials and a variety of bold new paradigms.

Talk to drug developers about clinical trials and one word comes up repeatedly—unsustainable. The expanding timelines, size, failure rate and cost of trials (**Tables 1** and **2**) have finally reached a point where, like the towering US debt, nobody can pretend it is viable. What's most distressing is the large number of compounds that earn kudos in phase 2 only to fizzle out in one of those big, outrageously expensive phase 3 trials (**Table 3**). Although it's by no means the only example, the trajectory of Sanofi (Paris)/Bipar's (now part of Sanofi) flaunted poly(ADP-ribose) polymerase 1 (PARP1) inhibitor tells the story. Hailed as spectacular by some after the phase 2 trial results in triple-negative breast cancer, the small molecule bombed in phase 3, the results of which were announced early last year.

The escalating expenses associated with clinical work are so ruinous, an industry that is renowned for sticking to the status quo is considering making extraordinary changes to the way it goes about R&D. "The issue goes even beyond clinical trials. The old way of doing biomedical research and drug R&D are not feasible anymore," says John Wagner, vice president of clinical pharmacology at Merck Research Laboratories (Whitehouse Station, NJ, USA). That realization is leading to a startling revamp of the clinical trial process.

What's in the works are new approaches, novel tools and an unprecedented focus on collaboration, even among the fiercest competitors, because pretty much everyone is in the same boat. All of this is being done in step with the US Food and Drug Administration (FDA), of course. "We want to support the development of new methodologies, but we need to work with FDA to make sure new ideas are embraced by reviewers," says Kelly Lai, director of science and regulatory affairs at the Biotechnology Industry Organization (BIO) in Washington, DC. The bold pioneers designing the new landscape admit it will still take some years to see how it pans out, but big changes are already visible.

(Source: INBIOMEDvision)

Picturing the problem

According to consultants CMR International (London), there were twice as many development projects halted in phase 3 during 2008–2010 than in 2005–2007 (ref. 1). In phase 2, where historically most drugs fail, success rates dropped to a mere 18% in 2008–2009, from 28% in 2006–2007 (ref. 2). Closer analysis reveals a lot. Of 108 failed phase 2 trials, more than half the stumbles were due to insufficient efficacy, almost 30% were related to strategy (insufficient consideration to similar drugs in development elsewhere) and another 20% hinged on clinical or preclinical safety (**Fig. 1a**).

Table 1 Rising protocol complexity and burden (all therapeutic areas, all phases of development)

	2000–2003	2004–2007	2008–2011
Unique procedures per protocol (median)	20.5	28.2	30.4
Total procedures per protocol (median)	105.9	158.1	166.6
Total investigative site work burden (median units)	28.9	44.6	47.5
Total eligibility criteria	31	49	Not available
Median number of case report form pages per protocol	55	180	Not available

Source: Tufts Center for the Study of Drug Development (CSDD). http://csdd.tufts.edu/.

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Table 2 Development costs for NMEs and biologics approved 1990–2008

	Direct costs ($ millions)	Percent of total cost	Capitalized costs ($ millions)	Percent of total
Basic research through preclinical	60	17	186	15
Clinical through regulatory approval	109	34	189	15
Allocated failures	166	49	866	70
Total per approved drug	355		1,241	

Source: Tufts CSDD

Commenting on these results, the author pointed to the high number of strategy-related bombs and wondered whether "an increase in collaborative efforts between companies up to the point of proof-of-concept for novel targets or mechanisms might be more cost-and-time effective." Such a suggestion would have been deemed ridiculously naive just a few years ago.

An analysis of 83 failed phase 3 programs revealed that many failed trials involve agents with novel mechanisms addressing high unmet need[3] (**Fig. 1b**). But in his analysis, CMR's science director John Arrowsmith also attributed much of the blame to "wishful thinking," which is clearly a problem. Experts also point to myriad other factors, including incompetence of those running the trials, poor recruitment practices, variability in diagnostics, inefficient protocol design and patient heterogeneity.

Many of these issues have plagued the industry for decades. The relatively poor track record in performing successful trials of companies from the biotech sector, compared with big pharma, is thought to relate to a lack of resources, insufficient expertise and care in trial design, overambitious timelines and underpowered studies. At the same time, the bar has been rising ever upward, forcing companies to do bigger and bigger trials that take longer to complete and cost astronomically more. This problem is particularly acute in cardiology. Eric Topol, chair of innovative medicine at Scripps Clinic (La Jolla, CA, USA) described the current situation as the "megatrial world," where tens of thousands of patients are enrolled to determine whether a drug works in all people[4] (**Table 4**).

Whatever the cause, the rate of new molecular entity (NME) approvals has been falling in the past decade. The FDA approved just 19 NMEs in 2009 compared with 53 in 1996 (ref. 5). Thus, even though 2011 has proven to be a banner year for drug approvals, including innovative medicines, the trend over the past decade has been disheartening (**Fig. 2**).

The cost of development for a drug is also now pegged at over $1 billion and estimates run as high 15 years to get a drug candidate from target identification to market[6]. Although R&D budgets grew dramatically over the past decade, beginning in 2009, there has been a downturn in such spending. Some attribute that fall to a growing sense that R&D is not providing sufficient return on investment[1]. Most of the expense in R&D arises during human testing.

Pain points

One hurdle, especially as trial sizes have swelled, has been data management. "One of the biggest trends we are seeing is the use of technology to run and manage trials," says David Levin, a vice president at Clinipace (Morrisville, NC, USA), a contract research organization (CRO). His company made the decision to invest in their own technology solution several years ago, and since then, he says, he's seen many more CROs make the leap to electronic data capture (EDC). The results have been gratifying. "It used to take our industry 90 days to process the data, clean it and make sure it was up to snuff," he says. Now, Clinipace can do that in two weeks, and sometimes even faster.

"The migration [to EDC] is clearly under way now," agrees Josef von Rickenbach, chairman and CEO of Parexel International (Boston), one of the world's largest CROs. "We've seen steady growth in demand for domain-specific IT products and services." It's not clear how widespread that ability is, however. As *ClinPage* editor Mark Uehling points out, now that so many aspects of clinical trials are automated, the challenge is to make sure all those tools mix and match. "We don't know how smoothly that is going and what is happening on the data integration end" (**Box 1**).

Uehling also points to an antiquated system of protocol design that has led to wide variation

Table 3 Selected phase 3 clinical trial flops

Product	Indication	Developer	Acquirer or licensee	Price paid by licensee or acquirer ($ millions)
GVAX (autologous tumor cells transduced, by a nonreplication competent retrovirus, with granulocyte-macrophage colony-stimulating factor)	Cancer	Cell Genesys	Takeda	50
Flurizan (tarenflurbil, a gamma secretase inhibitor)	Alzheimer's disease	Myriad Genetics	H. Lundbeck	100
Trovax (a modified vaccinia Ankara poxvirus vector engineered to express the 5T4 fetal oncoprotein)	Renal cancer	Oxford Biomedica	Sanofi	39
Asentar (capsule formulation of calcitriol)	Androgen-dependent prostate cancer	Novocae	Schering-Plough	72
Dimebon (latrepirdine, a small-molecule modulator of mitochondrial function)	Alzheimer's disease	Medivation	Pfizer	225 (includes milestones)
Ocrelizumab (humanized anti-CD20 mAb)	Alzheimer's disease	Roche/Genentech	NA	NA
Vadimezan (ASA404, an analog of flavone acetic acid that modulates nuclear factor kappa B and reduces blood flow)	Non–small cell lung cancer	Antisoma	Novartis	75
Elesclomol (STA-4783, a small-molecule inducer of Hsp70 and blocker of actin filaments and microtubules)	Metastatic melanoma	Synta	GSK	80
Iniparib (small-molecule PARP1 inhibitor)	Breast cancer	BiPar	Sanofi	500
Figitumumab (a fully human IgG2 mAb against IGFR)	Non–small cell lung carcinoma	Pfizer	NA	NA

Source: Hammer Stock Blog and Fierce Biotech. http://www.hammerstockblog.com/lessons-learned-from-sanofi%E2%80%99s-failure/.

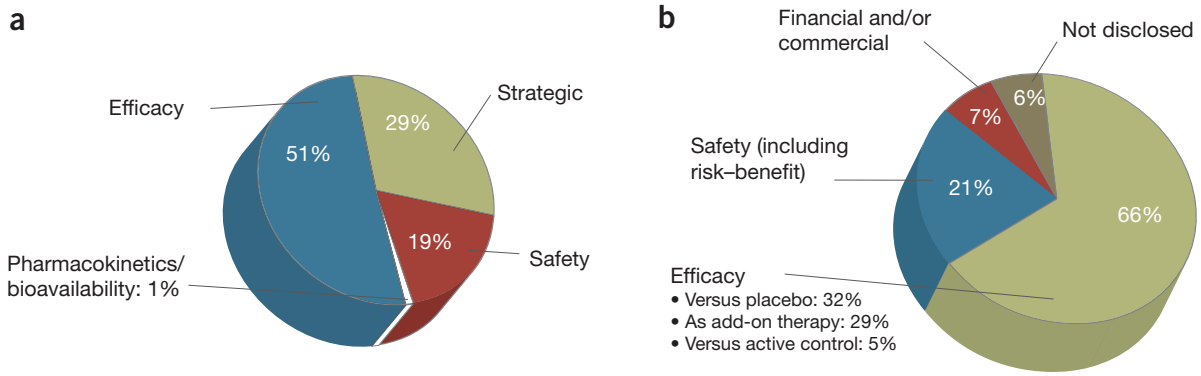

Figure 1 Reasons for clinical attrition. (**a**) Failures in phase 2. (**b**) Failures in phase 3. (Reprinted from refs. 2 (**a**) and 3 (**b**).)

in trial efficiency and a large number of amendments. One recent study by the Tufts Center for the Study of Drug Development (Boston) found that more than 40% of protocols are amended before the first visit by the first trial subject, and one-third of those amendments were avoidable[7]. This not only adds to the time and cost but can also completely derail trials by affecting the statistical analyses and thus the outcomes.

And getting data faster doesn't help if the trial has been mismanaged. Laurie Halloran, president of Halloran Consulting Group (Boston), says she still sees far too many cases where companies are either not scrupulous or are trying to save money and end up compromising their trials. "A clinical trial is a million moving parts," she says, and she has observed everything from gross incompetence (the wrong type of physician asked to recruit patients) to wasting money due to flawed protocols (a protocol that requires letters be sent by overnight mail to hundreds of physicians when an e-mail message would suffice).

The progress in EDC so far has been a "huge milestone" she says. "But that doesn't change the result if the doctors don't understand which patients should not be enrolled." There is still some element of "this is how we do it," Halloran says. Some companies put great effort into standardizing operating procedures, but still have employees with different titles but overlapping responsibilities. The pursuit of standards will have to be broad-ranging to have a big impact.

There will be new challenges ahead as CROs evolve and their relationships with companies change. Big pharma has been outsourcing more and more of the drug development process, von Rickenbach says. Early-stage companies, meanwhile, are increasingly using consultants across the product life cycle.

Scientific, competitive and financial pressures have also made drug development and marketing a global process. "Biopharmaceutical companies are increasingly launching their new products in multiple regions as a way to speed up their overall market penetration," he says. The relationships between CROs and drug developers are thus becoming much more strategic, depending on specific needs and fit. The changes are visible throughout the process, and happening faster than ever before.

Bold steps at the NCI

Another trend is an emphasis on standardizing operating procedures, demonstrated by work being done at the US National Cancer Institute (NCI). The agency started at the beginning, by reviewing procedures for clinical trial activation—the formal start of a clinical trial—and then made recommendations to accelerate that process, which traditionally has taken about two years for phase 3 trials and more than 500 days for phase 1 and 2 studies.

The changes affect policies, procedures and operations, including a recommendation for real-time project tracking systems. NCI is aiming for phase 3 trials to be activated within 300 days, and phase 1 and 2 studies within 210 days.

NCI has adopted a 'drop dead' clause (24 months for phase 3, and 18 months for phases 1 and 2) requiring trials to be canceled if they have not reached activation in time. The institute wants to cut the average trial activation time by 50% overall. Just as important, NCI is finally implementing a unified clinical data management system across all its 2,000 participating sites. "If they are doing an NCI-supported trial, all our cooperative groups will log into a website and see the same thing," says James Doroshow, director of the Division of Cancer Treatment and Diagnosis at NCI. In the past, each group could use their own software "and everyone had their favorite," he says. NCI is paying for the new software, which is 'pharma grade' and compliant with FDA regulations. Perhaps the biggest step is that investigators will have to share all their data.

The data management project is designed to generate obvious payoffs quickly. "If we have a drug from company X and we are doing eight trials, we need to be able to see if there are common toxicities or common characteristics to any tumors that are responding," he says.

NCI is also hoping to accelerate the move to standardized laboratory protocols for analyzing biomarkers. "You can take the top-tier academic medical centers and the same series of tests are done there, but you get different answers," he says. "We've been arguing about how to do HER2 testing since as long as it's been around"[8].

Table 4 Examples of phase 3 'megatrials'

Therapy	Drug class	Sponsor	Number of phase 3 trials	Number of patients in largest trial
Acacetrapib	Cholesterol ester transport protein (CETP) inhibitor	Merck	2	30,000
Dalcetrapib	CETP inhibitor	Roche	3	15,600
Dabigatram	Thrombin inhibitor	Boehringer Mannheim	11	18,113
Apixaban	Thrombin inhibitor	BMS/Pfizer	10	18,199
Rivaroxiban	Thrombin inhibitor	J & J/Bayer	15	15,527
Prasugrel	Thrombin inhibitor	Lilly/Daichi Sankyo	15	13,619
Sitagliptin	Dipeptidyl peptidase 4 (DPP4) inhibitor	Merck	82	14,000
Vildagliptin	DPP4 inhibitor	Novartis	70	3,118

Source: Ben Bonifant and Jeff Stewart, Campbell Alliance, Raleigh, North Carolina, USA

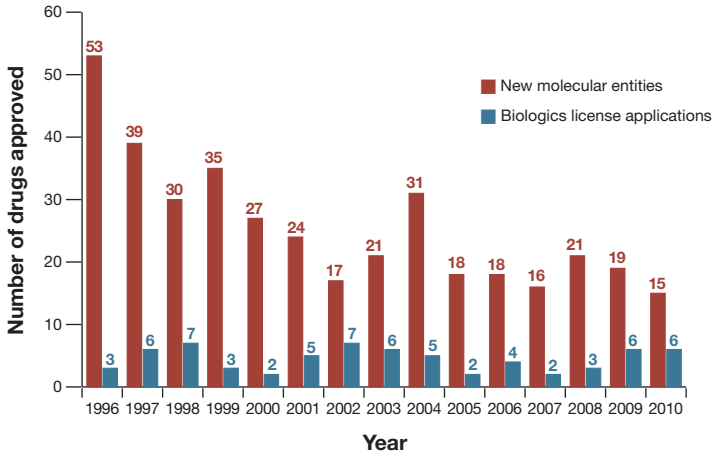

Figure 2 FDA drug approvals per year. (Reprinted from ref. 24.)

Working with the National Institute of Standards and Testing, NCI aims to produce some of these standards, validate them, then make them freely available. Another project involves working with major cancer centers to coordinate the validation of assays that diagnostic companies and others have developed but can't afford to validate. Doroshow says the agency has sufficient resources to do about 5–10 of these per year for the next couple of years.

Going virtual

New York–based Pfizer is also making a splash with new technology to recruit patients faster and in a more standardized fashion. The drug giant is using Exco InTouch's (Nottingham, UK) 'Recruit' text messaging technology in a pilot study for the overactive bladder drug Detrol LA (tolterodine). It's another first that required careful coordination with the FDA and has received a lot of attention. The tool is integrated with Pfizer's volunteer database and allows immediate text message–based communication and assessment of a subject's suitability within 5–10 min.

Figure 3 Your clinical trial is texting you. Exco InTouch eDiary tool provides a mobile technology platform with a user-friendly interface to make participating in trials easy, even remotely. Patients complete diary questionnaires through a series of text messages sent through their own cell phones. (Source: Exco InTouch)

Messages, such as 'Text YES to 54321 to Participate' are sent to patients, and responses go directly to Pfizer's recruitment staff who can make immediate decisions. The system is able to process over 500 messages per second. It can also be used to send protocol-specific messages to patients already enrolled in trials (**Fig. 3**). That so many cumbersome steps—reaching the right patients, screening them, enrolling them and then monitoring them—can take place almost instantaneously would be a huge boon.

Raymond Woosley, president and CEO of Critical Path Institute (C-Path; Tucson, AZ, USA)—a nonprofit organization established in 2004 to facilitate collaboration between regulators, the drug industry and academia—sees this 'virtual trial' as the future of clinical trials. The fact that Pfizer is testing the technology means it is more likely that there will be lots of 'fast followers' behind. C-Path's Electronic Reported Outcome Consortium is their biggest initiative, with 25 companies involved, according to Woosley.

Taking this concept to the extreme is Transparency Life Sciences, which is almost entirely web based. Founded in 2010 by Tomasz Sablinski, a former pharmaceutical R&D executive and the managing director of clinical development for the private equity firm Celtic Therapeutics (St. Thomas, US Virgin Islands), Transparency is focusing on finding new indications for generic compounds. They will select an indication, then post the information about the drug with indications and a clinical study outline on the web, asking for patients, drug developers, doctors and others to help design the protocol.

"Forget trials that have 25 end points," Sablinski says. "And measure only what you will really analyze." The trials will employ tests that can be done at home, using remote monitoring devices. According to Sablinski, most clinical studies "fit into this 75% or more remote data-collection category." Transparency is currently testing its website with a small group of contributors and expects to launch two to three projects in the upcoming months, focusing first on autoimmune, central nervous system (CNS) and cardiovascular diseases. He hopes the lower cost of the trials will attract foundations and venture capitalists.

The placebo conundrum

An issue that haunts clinical trials is the placebo effect, increasingly a factor particularly in CNS indications[9], where mental state can be difficult to assess and is influenced by higher brain function. As a result, even impeccably run trials fail because of a placebo effect that is too high.

MedAvante (Hamilton, NJ, USA), a CRO with a focus on assessing mental health, reports that over the past 25 years, the number of patients improving in placebo arms of trials for anxiety, depression and psychosis rose from 20–30% up to 40–50%, leading to many failures. The problem, says Mike Detke, MedAvante's chief medical officer, is that some patients enrolled in these studies aren't sufficiently sick. In addition, physicians' rating of patients can vary widely. If the patient's initial evaluation is flawed, a "change" in mental state may not be accurately reflected. Evidence exists that the patients who are less sick do better on placebos relative to effective treatments. The bottom line is "The bigger the placebo effect, the harder it is to see the effectiveness of your drug," says Detke.

To combat this, the company uses centralized raters who conduct patient interviews by means of video- or teleconference. "Centralized readers are standard for so many other tests, such as EKGs and measuring tumor size," he says. Because psychiatric diagnostic scales can be interpreted differently by different individuals, it makes sense to centralize and standardize their interpretations as well.

MedAvante has done five studies comparing centralized to site-specific psychiatric testing. "In studies of three drugs, we substantially increased the signal-to-noise ratio," he says. "The other two drugs proved not to be effective, but using centralized testing we reduced the placebo effect by 37% and 56%." The company believes the placebo effect may be sinking as many as 30–40% of CNS drugs undeservedly. They have completed more than a dozen clinical trials already and are working on many more.

Although MedAvante focuses on CNS studies, this approach may be useful in a broader range

Box 1 Electronic data capture

Many clinicians are still stuck firmly in the pen-and-paper era, avoiding where possible the use of electronic health records, let alone EDC. That, at least, is the view of Peter Coveney, professor of computational science at University College London, and principal investigator of a European project, INBIOMEDvision, which is bringing biomedical informatics researchers and clinicians together to discuss bioinformatics and medical informatics as common concerns. Although EDC technology is increasingly sophisticated, many, if not most, of the programs available are not yet user-friendly enough to appeal to a busy, stressed, nonspecialist clinician. "A system must be as quick and easy to use as pen and paper…with the ability to generate a referral letter, for example, by the click of a mouse," says Coveney.

And although EDC is much more common in the context of a clinical trial or other research setting than in routine clinical practice, even this is not yet completely widespread. A recently published survey of the use of EDC in clinical trials in Canada by Khaled El Emam of CHEO Research Institute, Ottawa, using data from 2007, found that only 43% of trials used some form of EDC[23]. "That figure will have increased steadily in the past four years, but take-up is still nowhere near universal," says El Emam. One innovation that may further increase take-up is the introduction of point-of-care clinical trials, where the decision to enroll a patient in a trial is taken at the point when a clinician decides that no over-riding reason exists to prefer either treatment under study. This is only feasible if randomization, treatment and data collection can take place seamlessly at the patient's bedside. However, El Emam adds, "With each trial sponsor using a different set of software packages, there may be several such systems in operation in any one hospital at a given time, making it much harder to transfer data or patients or make links between trials."

This lack of data standardization both within and between hospitals is often identified as a barrier to both the take-up and the efficient use of EDC systems, and Coveney has even linked it to London's disappointing performance in cancer outcomes compared to those in other parts of the country. "Cancer services in London are fragmented between sites and hospitals, and with no overarching [EDC] system, it is easy to lose track of patients or data."

But the UK experience in another discipline, neonatology, gives a clear example of the research benefits of an automatic, standardized system for patient data collection. Data from each of the 60,000–70,000 newborn babies who enter neonatal units in the UK each year—about 10% of all UK births—are now collected routinely at the point of care and stored in the Neonatal Data Analysis Unit (NDAU), based at Imperial College, London. Three types of data are collected: static (e.g., a baby's birth weight), regular (e.g., a temperature reading) and episodic (e.g., an infection). Links between the babies and their data are maintained using encrypted National Health Service numbers as identifiers.

Data stored in the NDAU are used in standard clinical care, as babies are transferred between units; in keeping long-term outcome records of babies who need specialist care; and for clinical research, as Neena Modi, the lead researcher on the project, explains. "With a complete, standardized set of records, identifying babies who fulfill the criteria for a particular clinical trial becomes straightforward. And linkage of our database to National Health Service Hospital Episodes statistics gives us the opportunity to capture long-term outcome data, which is crucial to many clinical trials involving infants and children, simply and cheaply," she says.

Most late-phase clinical trials involve large numbers of clinical centers, very often crossing international boundaries. Analysis of trial data can be hampered by discrepancies in data formats, which can be as simple as differences between field names or units. "We need to standardize data formats for interoperability, at least across Europe, if not worldwide," says Coveney. "There is a conflict between 'perfect' standards, which are almost impossible to define, and 'as good as' standards, which are easier to implement but cannot be universal." Some disciplines are adopting their own specialized standards and conventions, including the Digital Imaging and Communications in Medicine standards for the storage and transfer of digital images in biomedicine. And Patricia Lawford from the University of Sheffield, UK, a partner in the VPH-SHARE project (Virtual Physiological Human: Sharing for Healthcare—A Research Environment), which is collating and standardizing clinical data from disparate sources, explains another cause for concern: "Data protection legislation differs even across Europe, and what is permitted in one jurisdiction may not be in another."

Legal and ethical issues, such as privacy and data protection, can be particularly difficult when data are stored in the cloud for use by, for example, research partners in a clinical trial. Full anonymization, in which all trace of a link between the patient and the data is lost, will not be possible if data are to be used to aid selection of patients for clinical studies or if individual patients are to benefit from that research. There are also difficulties with anonymization, let alone pseudo-anonymization, as it can be possible to identify an individual from, for example, facial characteristics identified in a computed tomography scan. "A lot of research has gone into the manipulation of facial images to prevent this without damaging the essential clinical data," says Lawford. The increasing affordability of genomic information, and its consequent incorporation into clinical trials, adds to the difficulty of ensuring privacy; it has been estimated that it may be possible to identify an individual from no more than 75–100 single-nucleotide polymorphisms. Patients, however, are often keen to participate in clinical studies and to share their data—even genomic data. Harnessing the enthusiasm of internet-savvy 'expert patients' may prove useful in minimizing some of the main privacy concerns. Patients' representatives are other likely enthusiastic participants. "I would love to see the parents of newborns driving our research agenda," says Modi.

It may be that one of the barriers to universal uptake of EDC in the hospital community is that, in hospitals, information technology has historically been seen as a mundane but necessary part of the infrastructure rather than an essential research tool. Its use is finally becoming more widespread, however, and, with the development of open-source software, such as OpenClinica (Waltham, MA, USA), now used by over 12,000 researchers worldwide, it is reaching far beyond the well-funded hospital environment. And much is possible using simple, portable technology. An international team led by Brigitte Walther in the Gambia and funded by the UK's Medical Research Council recently concluded that a simple EDC system involving data entry with a netbook, personal digital assistant or tablet PC was faster and no less accurate than paper-based methods in collecting clinical research data from often remote rural settings in West Africa.

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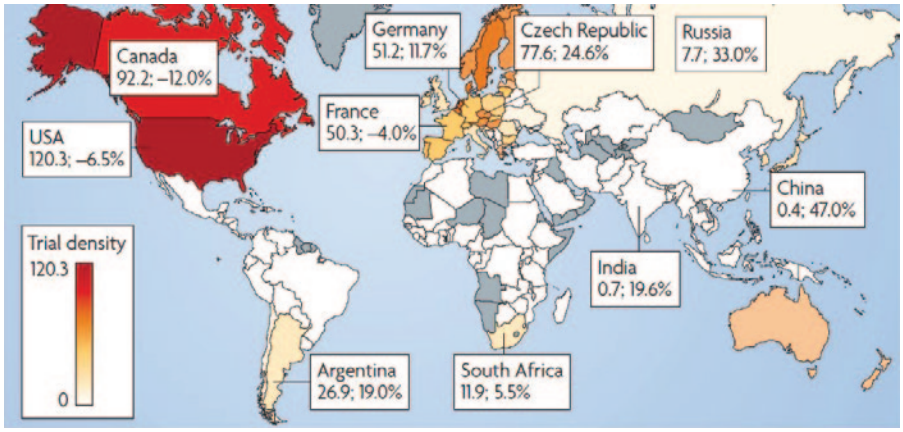

Figure 4 Density of clinical trials worldwide. Trial density is indicated by color, with the darker color having higher densities. Annual growth rate is indicated for some countries. (Reprinted from ref. 25.)

of diseases, as the role of higher brain function in other conditions comes into focus. Irritable bowel syndrome (IBS), for example, is a disease where the placebo effect plays a major role. In one striking study, nearly 60% of patients showed significant improvements in symptoms after taking a pill they knew to be a placebo[10]. This percentage is higher than most placebo effects in typical trials, which are in the 30–40% range for IBS. In a meta-analysis of 45 placebo-controlled randomized trials for IBS, the placebo effects varied from 16% to >70% (ref. 11).

Although the placebo effect is particularly problematic in testing drugs for pain and depression, its impact has been so pervasive that there is growing interest in it. Recently the Foundation for the National Institutes of Health (FNIH) carried out the Placebo Response Drug Trials survey to determine how much data pharmaceutical companies have for studying this. Although it appears there is ample information to conduct retrospective studies, no concrete next steps have been decided upon to do so.

Out of country

By far the biggest challenge facing clinical trial organizers is patient recruitment, particularly as trial sizes increase. This has led to the rapid and expansive growth of overseas trials, according to Charlene Sanders, vice president of global regulatory affairs at Premier Research Worldwide (Philadelphia; **Fig. 4, Table 5**). The Associated Chambers of Commerce and Industry of India reports that only a single clinical trial was outsourced to India by US-based drug firms between 1996 to 2000, but in the following five years, >190 such trials were conducted in India[12]. A recent US Department of Health and Human Services report found that in FY 2008 80% of approved drug marketing applications included data from foreign trials and over half of trial subjects and sites were outside the United States[13].

This trend is driven by the increased demand from regulatory agencies for more measurements or data on more patients, as well as the expansion of personalized medicine and research in new, often rarer, diseases. "With biologics, we are seeing companies going further and further afield to get the right population to test them," Sanders says. If a condition has a genetic component, such as multiple dystrophies or celiac disease, you'll find more such patients in populations with particular ancestries.

Increasingly trials with several thousand patients or more are being undertaken. This is more common when companies are testing 'me too' drugs in the population at large. "The developed healthcare markets of the United States and Western Europe are fairly saturated in terms of clinical research and there is intense competition for patients in many therapeutic areas," says von Rickenbach. That makes countries with big populations, such as the BRIC (Brazil, Russia, India and China) nations, attractive sites for trials.

Not surprisingly, this migration leads to new hurdles as well. Basic things, such as refrigeration or long-term clinical follow-up, can be a big challenge in an emerging economy. Standards of care and co-morbidities (e.g., the prevalence of tuberculosis or parasites) are also important considerations. Consent can also get much trickier, as societies have different traditions about who can make such decisions on behalf of an individual.

Seeking to improve its oversight of overseas trials, FDA would like to require standardized electronic data formats and stronger relationships between the agency and other organizations overseeing drug development in other regions.

Biomarker boondoggle?

Patient heterogeneity presents another major challenge. Tolerx (Cambridge, MA, USA) and partner GlaxoSmithKline (GSK) found that out the hard way with otelixizumab, an investigational anti-CD3 humanized monoclonal antibody (mAb) licensed from BTG (London). Otelixizumab looked promising as a treatment for type 1 diabetes. A phase 2 trial, which included four years of follow-up, suggested it helped preserve beta cell function. Not so in phase 3 testing, however.

Whereas dosing may have been one of the issues, a likely contributor to the trials' failure is that residual beta cell function among diabetics differs depending on age of onset. Diabetics diagnosed before puberty suffer greater amount of damage than those diagnosed during or after puberty, according to Paolo Pozzilli, professor of endocrinology and metabolic diseases at the London School of Medicine and Dentistry[14]. "We need to do future trials in patients who are less heterogeneous," he says. "When the patients are so mixed, it is not easy to find an effect unless it is remarkable," he says.

Investigators have long been looking for ways to characterize and distinguish patient types. The massive success of drugs, such as Roche (Nutley, NJ, USA)/Genentech's Herceptin (trastuzumab) and Novartis' (Basel) Gleevec (imatinib) ushered in the era of targeted therapies and gave some hope that a wealth of such drugs, paired with accurate tests, could be discovered. "Blockbusters are becoming obsolete, and we are turning to niche busters," says Claudio Carini of Pfizer.

But finding those biomarkers has proven to be tough; the picture is clearly more complicated than most people thought. For one thing, nongenetic factors, such as prior treatment, can affect patient response. In addition, similar mutations appear to act differently in different tumors. BRAF mutations, for example, predict response to Zelboraf (vemurafenib; Roche) in melanoma treatment but not for colon cancer.

Adding to the problem is the lack of a clear pathway to approval for biomarker assays. As a result, the validated biomarker pipeline

Table 5 Number of countries participating in a given clinical trial

Phase	2002–2006 (mean number of countries)	2006–2010 (mean number of countries)
Phase 1	2	2
Phase 2	11	18
Phase 3	19	34

Source: Tufts CSDD

is pretty dry. A major step forward occurred last year when the FDA and the European Medicines Agency (EMA; London) formally accepted the use of seven renal safety biomarkers for preclinical use based upon data from the Predictive Safety Consortium (PSTC)[15]. The markers, Kim-1, albumin, total protein, beta2-micoglobulin, cystatin C and clusterin, were found to be more specific and sensitive than traditional markers, even though none of these 'new' markers were particularly novel—many had been known for decades.

Importantly, though, the PSTC not only represents an advance for preclinical renal testing, which has been fraught with problems, but also a regulatory pathway by which clinical biomarkers can be validated. Some markers under development have looked promising for years; now there is hope that they may soon be authorized for use in clinical trials. What's more, says C-Path's Woosley, "We have 50 biomarkers under review now."

Getting here required some contortions, however. "We have an agreement not to use the "v word," says Woosley, because the term 'validated' was so contentious. "Instead, we will ask the agency if the marker is qualified for a particular use." The group's work has thus created the concept of "rolling biomarker qualification," which is a less rigid approach but one that fits the agency's framework and the emerging complex science. This approach allows the agency to approve biomarkers for very specific uses, but still allow further research and data submission to support additional uses.

Despite all the attention being paid to biomarkers, the number of targeted therapies is still vanishingly small. Even so, some remain optimistic that this will change soon. "Over the next five years, we should see consistent results," says Pfizer's Carini. This summer's approvals of Genetech's Zelboraf for advanced melanoma and Pfizer's Xalkori (crizotinib) for lung cancer are hopeful signs. Both were approved for patients with specific mutations in their cancers. Zelboraf targets the BRAF V600E mutation whereas Xalkori targets abnormal anaplastic lymphoma kinase (ALK) production.

Adaptive trials

Smaller trials would be a boon to drug developers, as not only do costs go up with the number of subjects, but also per-patient costs have risen. According to a recent report from Cutting Edge Information, per patient costs have gone up an average of 70% across all phases since 2008 (ref. 16). The largest increases were in phase 3a and 3b trials, where per patient costs now top $40,000.

Adaptive trials provide one answer to spiraling costs. These trials typically are done using small cohorts quickly and the flexible protocols allow researchers to make adjustments to certain parameters, like doses, the number of arms or accrual rates, in response to data that are captured during the trial. "If the low dose isn't having any effect, why keep it? And if you are seeing side effects why go on?" Woosley says.

This goes against the traditional approach of sticking like glue to the original trial plan, but pioneers counter by saying that exploratory adaptive trials can speed drug development without raising regulatory red flags. "As long as patient safety is never compromised, FDA is showing a lot of leadership in these new innovative approaches," says Clinipace's Levin. Such novel trials designs are a powerful tool to fail bad drugs more quickly, and get information to guide the design and execution of phase 3 trials.

The pioneering I-SPY and BATTLE trials are large collaborative efforts, which are testing multiple drugs while looking for response biomarkers in breast cancer and lung cancer therapeutics, respectively[17]. In I-SPY 2, which was launched in March 2010, patients have all had chemotherapy and have invasive breast cancers and receive the standard of care. Most also receive an investigational agent from Abbot Laboratories (Abbott Park, IL, USA), Amgen (Thousand Oaks, CA, USA) and Pfizer. The drugs include the following: veliparib (ABT-888), a small-molecule inhibitor of PARP1; conatumumab (AMG 655), a human mAb against APO/TRAIL (tumor necrosis factor–related apoptosis-inducing ligand); AMG 386, a peptibody Fc fragment linked to a peptide that inhibits the pro-angiogenic factors angiopoietin-1 (Tie-2) and angiopoietin-2; figitumumab, a fully human IgG2 mAb against insulin-like growth factor receptor (IGFR); and neratinib (HKI-272) a pan-ErbB (HER2 kinase) inhibitor. Over the entire course of the trial, 12 drugs will be evaluated and multiple markers followed.

"Part of the beauty of it is how quickly we can cycle drugs in and out of the trial," says Laura Esserman, a professor and clinician at University of California, San Francisco's Comprehensive Cancer Center, who helped conceive and launch I-SPY. It takes only about two months to get a new drug approved by the project's institutional review board. Esserman says that three new drugs are already approved for use in the trials: a vascular disrupting agent, insulin growth factor plus metformin and a drug targeting phosphatidyl inositol-3 kinase.

Under an unusual master investigational new drug (IND) approval from FDA, the investigators are able to graduate, drop and add new compounds to the trial without needing to write new protocols. The aim is to "shave several years and hundreds of millions of dollars off the current process," according to a press release from FNIH's Biomarkers Consortium, a member of this unique collaboration, which includes FDA and dozens of cancer centers.

Shortly after I-SPY 2 launched in 2010, MD Anderson Hospital (Houston) announced some results from its groundbreaking BATTLE phase 3 trial in non–small cell lung carcinoma at the Annual Meeting of the American Association for Cancer Research held in April 2010 in Washington, DC. Drugs tested included Roche/Genentech's Tarceva (erlotinib), Pfizer's Nexavar (sorafenib), Eli Lilly's Zactima (vandetanib) and Tarceva with Targeretin (bexarotene). Results suggested that each drug worked best in patients whose tumors shared specific molecular signatures. For example, patients with *KRAS* mutations seemed to respond best to Nexavar, whereas Tarceva was more effective against epidermal growth factor receptor (EGFR) mutations. Zactima was best with high vascular endothelial growth factor receptor 2 (VEGFR-2)-expressing tumors. And Tarceva with Targeretin was most potent in patients with cyclin D1 defects or EGFR gene amplifications.

Those results were published last June[18], the same month BATTLE II was launched with about 20 patients. BATTLE III, which examines targeted frontline therapy of hard-to-treat tumors was launched in May 2011. The trial aims to find new marker and/or targeted therapy combinations for those 80% of lung cancer patients who do not have either of the known markers—EGFR or ALK-fusions.

Both I-SPY and BATTLE trials require tissue samples from patients and employ a Bayesian adaptive randomization statistical model pioneered by MD Anderson's Don Berry. Whereas the approach is not yet widespread, it does seem to be gaining traction. For example, this spring Eli Lilly (Indianapolis) launched a high-profile phase 2 adaptive trial of litronesib, a small-molecule inhibitor of the kinesin-related motor protein Eg5. Phase 1 data and various preclinical models indicated the drug has broad activity across tumor types and single agent activity, according to Eric Westin, senior director of Lilly Oncology. Lilly is now testing the drug in a trial that includes six arms, with only 15 patients in each one. But each arm can include patients with non-small cell lung, ovarian, prostate, colorectal, gastroesophageal, or head and neck cancer. The investigators will be measuring tumor response as well as progression-free survival.

More patients will be added to the trial if positive data emerges. "It's an indication-finding trial," says Westin, who points out that both efficacy and side effects could be specific to tumor type. "Head and neck patients, for example, are more likely to have prior radiation to the mouth, " he says. "We need to know

if that puts them at higher risk of side effects from this compound."

The researchers will also be collecting DNA from the tumors, and the trial will deliver data about putative gene expression–based signatures that were derived from xenograph models. The adaptive trial design, according to Westin, is especially well suited for drugs with single-agent activity because the signals will be less muddied then when you are using multiple compounds in one trial.

It's not just big pharma trying novel designs either. Ikaria (Hampton, NJ, USA), which is developing new critical care treatments, took that approach when they were investigating a treatment for kidney failure secondary to liver disease. Liver failure is what actually precipitates the kidney failure, and "these patients are very complicated and have lots going on," explains Douglas Greene, executive vice president of R&D at Ikaria.

The company was able to complete the trial using just two blood tests that determined whether the kidneys were functioning normally or not. "We discussed the design and we used a special protocol assessment," Greene says. Using survival data would have been pointless in this case and the well-established mechanism made FDA open to the novel design.

Box 2 Selected precompetitive collaborations

Several precompetitive collaborations have been set up in recent years to work on areas where companies have found it difficult to make progress individuals using proprietary data.

The Biomarkers Consortium. Public-private biomedical research partnership managed by the FNIH to discover, develop and qualify biomarkers to support new drug development, preventive medicine and medical diagnostics. Founding partners include the FDA, US National Institutes of Health, the Pharmaceutical Research and Manufacturers of America (PhRMA, Washington DC), the Centers for Medicare and Medicaid Services (Baltimore) and the Biotechnology Industry Organization (BIO). The group has launched at least ten projects in Alzheimer's, cardiovascular disease and breast cancer as well as other areas.

Innovative Medicines Initiative. A partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations that is aimed at speeding up drug development. It funds collaborative research projects and builds networks of industrial and academic experts. The initiative is currently funding 23 projects with a total of €450 ($588) million covering drug safety and efficacy, knowledge management, education and training. The group is also evaluating the 86 'expressions of interest' that came in response to the initiative's fourth call for proposals.

Clinical Trials Transformation Initiative. Founded by FDA Office of Critical Path programs, this public-private initiative includes more than 60 organizations including pharmaceutical and biotech companies, BIO and PhRMA, device and diagnostic developers, clinical research organizations, institutional review boards, academic institutions, multiple government agencies including the FDA. Hosted at Duke University (Chapel Hill, NC, USA), its mission is to identify practices that through broad adoption will increase the quality and efficiency of clinical trials. The group has projects looking at issues including IND safety assessment, improving the public interface for use of ClinicalTrials.gov, site metrics, central institutional review board use for multicenter clinical trials. Recommendations have been published for two of the projects: effective and efficient monitoring as a component of quality assurance in the conduct of clinical trials, and improving reporting of unexpected serious adverse events to IND investigators.

Critical Path Institute. An independent, nonprofit organization dedicated to implementing the FDA's Critical Path Initiative by creating collaborations among regulators (scientists from the FDA, EMA and Japan's Pharmaceuticals and Medical Devices Agency) and the regulated (medical product industry) that result in accelerated development of safe, new medical products. Established as a 'trusted third party' to enable collaboration between government regulators, the academic community and regulated businesses, C-Path manages industrial consortia of companies willing to share precompetitive knowledge and work in support of projects identified as high priority by the FDA. Twenty-five pharmaceutical companies are members. Projects include predictive safety testing, patient-reported outcomes and specific disease-related initiatives.

Sage Bionetworks' Arch2POCM. A new public-private partnership composed of academic, pharmaceutical industry and regulatory scientists and clinicians, public and private funders, and patient groups. The goal of the Arch2POCM partnership is to develop, use and make available safe test compounds against novel protein targets to take oncology, immunology and neuroscience projects from ideas to POCM, phase 2 clinical trials). Arch2POCM will operate as a distributed scientific and clinical network (the archipelago) including partnered pharmaceutical organizations, academic laboratories and institutions, US, EU and Canadian regulatory and funding agencies and patient-advocacy groups. All data and safe test compounds will be made openly available to the academic and pharmaceutical scientific community. The group plans to launch operations early in 2012 with an initial focus on cancer and two areas in neuroscience, autism and schizophrenia.

Precompetitive data sharing

Another startling development of recent years has been the wave of projects around pre-competitive data sharing (**Box 2**). "In the 1990s, we talked about precompetitive data sharing, and nobody was willing," says Woosley. "Then in 2004, Janet Woodcock and Mark McClellan said that the failure rate of trials is double [what it was in the previous decade], and suddenly people started talking about sharing."

Merck's John Wagner sees precompetitive collaborations as the key to success especially around biomarkers. The company has worked with AstraZeneca (London) on cancer markers and collaborated with several other pharmaceutical companies, including GSK, Eli Lilly and Roche, as well as government agencies, on a pivotal diabetes-related project. That effort was part of the FNIH's Biomarkers Consortium. The work pooled data from multiple trials and included results from more than 2,500 patients.

The analysis confirmed the predictive utility of adiponectin (a peptide hormone that regulates glucose metabolism in adipose tissue, among other things) across the spectrum of glucose tolerance as well as demonstrating that cross-company precompetitive collaboration is "a feasible and powerful approach to biomarker qualification"[19]. "Just think," says Merck's Wagner, "if we'd known that ten years ago, rosi[glitazone] and the other glitazones could have been used more effectively."

Similarly, Johnson & Johnson (New Brunswick, NJ, USA), GSK, AstraZeneca, Sanofi and Abbott are pooling data from 4,000 patients that were enrolled in 11 failed Alzheimer's drug trials. The project is spearheaded by the C-Path's Coalition Against Major Diseases (CAMD) and funded by the FDA and Science Foundation Arizona. Data from other drug companies and the US National Institutes of Health will be added to the pool as well, and the CAMD is planning to establish similar pooled databases for Parkinson's disease and tuberculosis.

Europeans may actually be a step ahead of Americans in this arena. The Innovative Medicines Institute (IMI; Brussels) "dwarfs everything else," says John Waterton, head of imaging at AstraZeneca. The project will be funded with $1 billion from the European Commission (Brussels) and $1 billion 'in-kind' support from pharmaceutical participants, which includes sweat equity. Pharmaceutical companies devise the requests for proposals and work with academic groups to address bottlenecks in drug discovery and development.

Dozens of ongoing projects are addressing bottlenecks through precompetitive collaboration in CNS, cancer, inflammatory, metabolic and infectious diseases. Waterton is leading IMI's Quantitative Imaging in Cancer: Connecting Cellular Processes with Therapy, which is focused on markers for phase 1 clinical trials. "That's the sweet spot," he says. The group will try to fish out "decision-making markers," for known candidates that are not yet well studied.

IMI and C-Path recently inked a memorandum of understanding that will help even the global playing field. The agreement signifies that the two groups are committed to finding ways to "leverage one another's work."

Perhaps the most intriguing and forward looking of these projects is Arch2POCM, which is still in its infancy but is taking on one of the biggest challenges—target validation. The name is a combination of archipelago and proof of clinical mechanism, and the goal is to create a shared database containing data on proper modulation of disease targets, without including patent claims. The database would also contain IND filings and test compounds. Stephen H. Friend, the founder of Sage Bionetworks (Seattle) and the leader of the Arch2POCM project, describes it as "a new paradigm."

Negative POCM data alone could save drug developers up to $12.5 billion annually, it is estimated, because they could stop wasting money running down the same blind alleys[20]. A 2008 *PLoS Medicine* article noted that more than half of the studies showing a drug was ineffective were never published in medical journals[21]. Key partners in Arch2POCM are the Structural Genomics Consortia at the University of Oxford in the UK and at the University of Toronto in Canada.

"No one company can build one of those maps of disease," Friend says. "They need more data." By "derisking" targets, "we build a common stream of knowledge," he continues. Companies can then compete off that stream to make profitable compounds. Like Transparency's Sablinski, Friend is a proponent of open-source knowledge and he sees this as a crucial development to speed drug development by fixing the very heart of the problem—the quality of the targets companies address. Having worked in academia and industry, Friend launched Sage Bionetworks in 2009, with the vision of creating an "open access, integrative bionetwork evolved by contributing scientists working to eliminate human disease."

In a project with AstraZeneca, Sage is developing advanced computational models of disease genetics that aims to help researchers better design trials and select patients. These models will be placed in Sage's public repository and available to all. A partnership with Merck on a database for cardiovascular and metabolic disease drug discovery will likewise generate data that are put into the public domain one year after the collaboration ends.

Biotech companies are conspicuously absent from the biggest of these precompetitive data-sharing exercises, but they are involved through the adaptive trials and other consortia. I-SPY2 study results will be made broadly available to the entire cancer research and drug development community. BATTLE's results will also benefit many competitors in the lung cancer arena.

The biggest payoff, however, might come from projects not yet begun. About ten years ago, FDA was trying to get pharmaceutical companies to share their phase 3 failure data so the FDA could take a systematic look at it. "Remember, we only look at drugs in great detail when a submission is made," says Robert Temple, deputy center director for clinical science at FDA's Center for Drug Evaluation and Research. "When drugs fail, we get a much more superficial look." It could be "very useful" to look at all those data together, he says.

Last April, FDA commissioner Margaret Hamburg said that rather than "just sit and watch them fail," FDA should disclose more about drug failures. Because FDA has information on every treatment ever submitted, the agency could mine that information to help solve key scientific questions in drug development[22]. Even if restricted to eliminating bad targets in notorious fields, such as sepsis, weight loss and dementia, sharing data about failures could have a tremendous impact.

Until that happens, Temple thinks developers will need to take many steps, such as looking at a wider range of doses, trying to "enrich" trials by excluding noncompliant or placebo -sensitive patients, and better use of biomarkers.

Virtual trials, data sharing and transparency are some dramatic changes, and it is all happening much more quickly than is usual in this industry. It's worth wondering whether in 10 to 20 years, clinical trials will look completely different from the way they do today. "I'm a big proponent of starting all over and doing it right," Woosley says. "Randomized controlled trials are out of date, and it's time to use the tools of the future."

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