REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

The Large Pharmaceutical Company Perspective

Michael Rosenblatt, M.D.

From Merck, Kenilworth, NJ. Address reprint requests to Dr. Rosenblatt at Flagship Pioneering, 55 Cambridge Pkwy., Rm. 800E, Cambridge, MA 02142, or at mrosenblatt@flagshippioneering.com.

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LARGE PHARMACEUTICAL COMPANIES CONDUCT CLINICAL TRIALS TO EVALuate efficacy and identify safety issues for candidate drugs as effectively, efficiently, and expeditiously as possible, while addressing simultaneously the requirements of regulatory authorities across the globe. To put the fewest people at risk and to learn the most, these trials often are configured to provide evidence for health care providers, regulatory approval, and reimbursement from health agencies. Because there are so many unknowns, pharmaceutical research and development is a high-risk business with the highest failure rate for new product candidates of any industry.

HIGH-ORDER COMPLEXITY IN OUTCOMES TRIALS CONDUCTED BY LARGE COMPANIES

The American libertarian L.K. Samuels wrote, "Complexity in a system tends to increase that system's inefficiency; the greater the number of variables, the greater the probability of those variables clashing, and in turn, the greater the potential for conflict and disarray. Because more can go wrong, more will."[1] Phase 3 outcomes trials conducted by large pharmaceutical companies are among the most complex experiments performed in medicine. In my opinion, it is this complexity that represents the single greatest challenge facing large pharmaceutical companies.[2,3] Although the hypothesis being tested may seem straightforward, the actual trial has many variables, is fraught with risk (both the scientific risk of experiment and the operational risk of implementation), and is often shaped by unexpected events that may be related not to the investigational drug but rather to the play of chance (Fig. 1, and see the interactive graphic, available with the full text of this article at NEJM.org).

An interactive graphic is available at NEJM.org

Success in this context requires broad expertise in the sciences fundamental to the therapeutic area being tested, talent in managing large and diverse teams, and a large, complex administrative apparatus. The activities of clinical investigators, protocol designers, statisticians, independent experts, project managers, institutional review boards, data and safety monitoring committees, manufacturers, quality controllers, suppliers, compliance officers, and others need to be orchestrated at multiple (sometimes hundreds) of trial sites in many countries. Many of these entities function under their own unique goals and rules.

Outcomes trials of treatments for chronic diseases must be conducted over several years in order to accrue clinically meaningful information. These longer study cycle times are an additional source of complexity, with challenges in recruitment and retention.[3] Failure to retain participants in a trial leads to the problem of "missing data" — which then becomes an issue in interpreting results on trial completion. Furthermore, "drop ins" (e.g., the patient's personal physician pre-

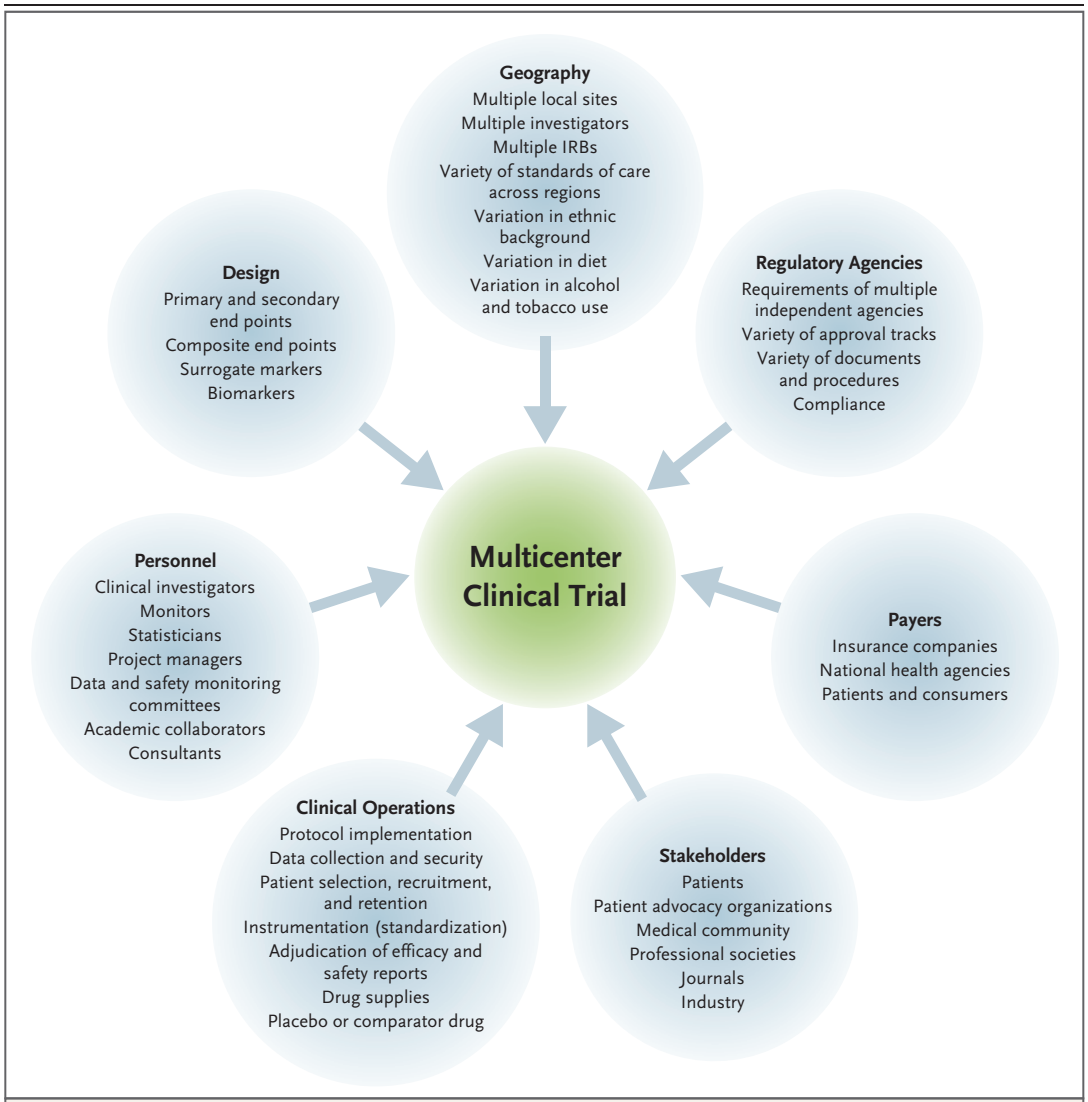

Figure 1. Factors Contributing to Complexity in Large Clinical Outcomes Trials.
IRB denotes institutional review board.

scribing other drugs to treat the target disease in the trial) may confound results.

Ironically, intellectual curiosity can compromise success. When trials are loaded with "wouldn't it be nice to know" analyses, complexity increases. As the number of variables tested increases, so does the potential for spurious findings.

In the decade from 2002 to 2012, clinical trials became much more complex. As shown in Table 1, the number of end points nearly doubled, and the average number of procedures that a trial participant underwent rose from 106 to 167 — an increase of 58%.[3] There are multiple factors contributing to the rise in complexity. First, trials must be designed to satisfy more "masters" (e.g., regulators, medical community, payers, and patients) than before. More countries are mandating as a condition of approval that cohorts from their country be included; racial diversity and inclusion of both male and female participants are also often required. The increased emphasis on clinical outcomes versus surrogate markers also adds to the duration and size of the trial — and complexity increases nonlinearly with size. Some trials face exceptional challenges — for example, looking for a suicide adverse-event signal in the context of a depression trial. More and more new agents are tested in the context of improved standards of care, so

Table 1. Increasing Complexity of a Typical Phase 3 Clinical Trial.*

Trial Design Characteristic	2002	2012
Total no. of end points	7	13
Total no. of procedures	106	167
Total no. of eligibility criteria	31	50
Total no. of countries	11	34
Total no. of investigative sites	124	196
Total no. of patients undergoing randomization	729	597
Total no. of data points collected	NA	929,203

* Adapted from Getz[3] and the Center for Information and Study on Clinical Research Participation. NA denotes not available.

trials need to be larger to show a clear advantage. This is particularly true in multinational trials in which the magnitude of the treatment effect may vary from country to country.[4,5] End points, too, have evolved: many are now composites of several clinical outcomes, particularly for cardiovascular events. When available drugs are effective but unmet medical need remains, it may not be ethical to conduct placebo-controlled trials. Trials comparing active agents are by nature more complex and riskier because larger groups are needed to show a treatment effect.[6]

Because medicine is taught by example, I present here two examples of successful phase 3 trials to illustrate some of the issues of complexity encountered in large outcomes trials. Despite issues that arose, the trials achieved their goals. Because all my direct experience with trials conducted by large pharmaceutical companies comes from Merck, I draw on that experience; similar examples could be drawn from the annals of any large company.

EXAMPLE 1 — THE ROTAVIRUS EFFICACY AND SAFETY TRIAL (REST)

In 2003–2004, rotavirus infection was the leading cause of severe gastroenteritis among infants and children worldwide, with approximately 500,000 children dying each year (accounting for 1 in 4 diarrhea-related deaths among children younger than 5 years of age) and more than 2,000,000 hospitalized annually because of the virus.[7,8] REST was a phase 3 trial that tested the pentavalent three-dose RotaTeq vaccine (Merck) in approximately 70,000 infants and children.[9] Knowing the history preceding REST is crucial to understanding the challenges in designing and conducting the largest pediatric vaccine trial since the Salk polio vaccine trials in the 1950s.

In 1999, after the phase 2a trial of RotaTeq was completed and planning for phase 3 was beginning, a rotavirus vaccine previously licensed in the United States, RotaShield (Wyeth Lederle), was voluntarily removed from the market because a rare side effect, intussusception (a disorder in which the bowel telescopes in on itself, often with a fatal outcome if diagnosis is not prompt and surgery timely), was associated with vaccination.[10] (Intussusception also occurs spontaneously without vaccination.) Intussusception was unanticipated: although there was a questionable signal before approval of the Wyeth vaccine, the increased incidence of intussusception was confirmed during postapproval surveillance.[11] Possible explanations were proposed post hoc, but no mechanism has been established. At the time, it was not even known whether natural rotavirus infection produced intussusception.

The three vaccines or candidate vaccines for rotavirus — RotaTeq, Rotarix (GlaxoSmithKline),[12] and RotaShield — were based on live viral constructs that differed from each other. The Merck candidate vaccine was developed in academia,[13] with subsequent development deriving from an academia–industry research collaboration.

Before the intussusception issue arose, a conventional phase 3 trial involving 6000 participants had been planned for RotaTeq. But withdrawal of RotaShield for safety reasons necessitated a totally new approach to development. The unexpected safety signal required an increase in the number of participants by an order of magnitude (to 70,000) in order to determine whether RotaTeq was associated with an enhanced risk (relative risk of approximately 2) of intussusception, an event that occurred in 1 to 3 of 10,000 immunizations in the Wyeth experience. Adequate data on background rates of intussusception were not available.

Despite this problem, the need for a rotavirus vaccine was compelling, although the benefit–risk ratio differed widely in the developed versus developing world. In developing countries, morbidity and mortality were much higher than in developed countries.

Were there reasons to believe that RotaTeq would prove to be safer than RotaShield? Supporting evidence was mostly indirect: a live, oral, viral vaccine would not be expected to cause in-

tussusception because rotavirus natural infection was not known to be associated with intussusception (subsequently, this proved to be incorrect). RotaShield produced fever in 20% of recipients; RotaTeq caused none — so it was less "inflammatory." And the RotaTeq viral construct had less uptake across intestinal mucosa and replication in the gut. If intussusception resulted from virus in the gut, an improved benefit–risk ratio was possible.

Whether intussusception would be a "class effect" for all rotavirus vaccines or would differ among vaccine constructs was not known. However, the need for an extremely large clinical trial oriented toward a rare safety issue was clear. REST targeted both efficacy and safety, but intussusception drove the design. The main objective was to show an acceptable level of safety, but the exact level was not known.

But how to power such a trial? An event-driven protocol with a group-sequential design was created. REST was designed to closely monitor for the rare prespecified safety event, intussusception, with continuous surveillance by the independent data and safety monitoring committee. The design used prespecified boundaries for observed events in vaccine recipients as compared with placebo recipients (Fig. 2).[14] If the observed difference reached the "unsafe" boundary at any time, the trial would be stopped. If the observed difference was within the region for an acceptable safety profile after at least 60,000 infants completed follow-up, then the trial would be considered successful. If neither boundary condition was reached, the data and safety monitoring committee would trigger enrollment of an additional 10,000 infants. The trial would proceed in this manner, passing through each "gate" with review and a decision to proceed or not by the data and safety monitoring committee after results from each additional group became available (up to a total of 100,000 infants).

The power and sample size for this event-driven protocol were determined with the use of Monte Carlo simulation. REST was designed to detect 10 cases up to 6 weeks after any dose of vaccine. The trial provided a high probability that an unsafe vaccine would be declared "unsafe" early, as well as a high probability that a "safe" vaccine would meet the acceptable safety criteria. (The profile for an unsafe vaccine was based on the increased rates of intussusception that were observed with RotaShield.)

After analysis of 60,000 participants, the results were in a "gray zone," so the data and safety monitoring committee recommended continuation of the trial. Ultimately, 70,000 children were enrolled, a number 10,000 larger than originally planned and much larger than in typical outcomes trials (which involve 3000 to 15,000 patients). Although the group-sequential design was ingenious, it placed unusual risk on the sponsor: the trial commenced without its size, duration, or budget being known.

The complexity of REST was formidable. There were approximately 500 sites in 11 countries. At one point, 200 children were enrolled daily. In most cases, dose 1 of vaccine or placebo was administered at the time of enrollment. Three doses of vaccine or placebo were administered at three separate visits 4 to 10 weeks apart. The minimum duration of monitoring for intussusception or serious adverse events was 1 year after the first dose. Participants in the efficacy cohort were followed for 2 full rotavirus seasons. The rate of loss to follow-up (a period of 6 weeks after the last of three doses) was less than 0.4%.

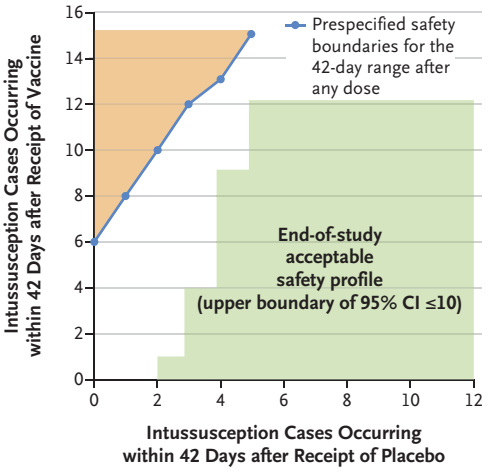

Figure 2. Design of the Rotavirus Efficacy and Safety Trial (REST).

The graph indicates the prespecified boundaries for acceptable safety or lack thereof with regard to the occurrence of intussusception. The safety level for intussusception associated with receipt of the vaccine versus placebo was acceptable if the plotted data fell within the shaded green area. Data above the solid line (shaded orange area) would be deemed unacceptable. Data between the shaded regions would indicate an indeterminate outcome (neither clearly unsafe nor clearly safe). CI denotes confidence interval. Adapted from Heyse et al.[14]

All cases of suspected intussusception were adjudicated according to carefully crafted criteria by a three-person, independent, blinded adjudication committee. Success hinged on "excruciating attention to detail," according to Heyse et al.[14] Adjudication was performed according to a prespecified case definition that required confirmation by radiography, surgery, or autopsy. Positively adjudicated cases were unblinded according to trial group by the data and safety monitoring committee, whose members made decisions regarding continuation of the trial. The committee met every 6 months during the trial.

REST showed the expected efficacy of the vaccine, and there was no substantial increase over background rates of intussusception, with six cases in the active-treatment group and five cases in the placebo group within 6 weeks after any dose (with no clustering of cases at any dose or time). In 2006, the vaccine was approved and recommended by the Advisory Committee on Immunization Practices for all U.S. children.

Once the product was licensed around the world, postapproval observational surveillance for intussusception suggested approximately 1 excess case per 100,000 children vaccinated.[15] Now at the 10-year anniversary of RotaTeq in the United States, there are 79 countries (36 of which are eligible for support from Gavi [the Vaccine Alliance]) that have introduced rotavirus vaccines in their national immunization programs. Rotavirus vaccines are available in more than 100 countries.

The benefit of vaccination proved greater and more rapid than anticipated because more cases of diarrheal illness in children result from rotavirus than originally attributed, and more children were protected than vaccinated owing to "herd immunity" in the presence of a ubiquitous virus.[16] In the United States, hospitalizations fell by 85 to 90% (40,000 to 50,000) per year among children younger than 5 years of age. The reports on REST[9] and Rotarix[12] in the *Journal* were selected as the 2006 research "papers of the year" by the *Lancet*.[17]

REST illustrates a unique role for large pharmaceutical companies. During the 1950s in the United States, the March of Dimes — a charitable organization — sponsored a polio vaccine trial involving more than 400,000 children, but since then very few trials of this magnitude have been sponsored by government, academia, or nonprofit organizations. When REST was initiated, there was widespread skepticism by academia and industry about the prospects for success; after all, a predecessor vaccine was withdrawn because of an unexpected, rare, serious side effect. And because the value of rotavirus vaccine was not yet fully understood, the potential benefit–risk ratio could not be accurately forecast. If intussusception was a "class effect" for live rotavirus vaccines, failure was certain. An up-front commitment for multiyear funding totaling hundreds of millions of dollars was required. Actually, more was at risk than generally appreciated because manufacturing facilities would need to be created and inventory generated without knowledge of whether they would ever be used. Overall, the risk of failure was high and was viewed by many as a nearly insurmountable barrier. In our current environment, this risk falls to large pharmaceutical companies.

From the industry perspective, there is no formula for calculating the costs of success versus failure in such circumstances. In addition to lost effort and investment in the case of failure, there is the "opportunity cost" of working on a failed project versus a successful one in the context of global competition. Yet the prospects of both public health and financial benefit made it possible for a pharmaceutical company to assume the risks, although it is important to remember that there have been many failures in similar situations.

In REST, a high-quality, independent data and safety monitoring committee was a key factor in the success of the trial. The committee had to decide at each prespecified time whether to continue and whether to expand the trial population. They unblinded every positively adjudicated case and decided whether to stop the trial on the basis of the prespecified stopping boundaries. Their involvement was unusually high, but they understood their charge and the trial went to completion. There are now two rotavirus vaccines licensed globally. In order to facilitate broad access, tiered (or differential) pricing has been used: vaccines are priced at differing levels appropriate to the value they create under the economic conditions in which they are used. As a result, countless children have been spared hospitalization or death. This gamble paid off.

EXAMPLE 2 — TRIALS OF ALENDRONATE

It is said that the greatest challenge preclinically is finding a good candidate molecule to start a

drug-discovery program, and the greatest challenge in clinical research is finding the therapeutic dose. Phase 1 trials, which usually involve a few healthy volunteers, seek to reveal frequent or severe drug-related side effects. Phase 2 trials focus on dose-ranging, often using a surrogate end point that predicts (with varying success) the clinical outcome to be tested in phase 3. Phase 3 outcomes trials usually focus on a single dose level (or limited number of dose levels) to examine efficacy and safety with the idea of providing direction for the clinical use of a treatment.

For alendronate, a bisphosphonate bone-resorption inhibitor for osteoporosis, the preferred dose was not discovered until phase 3 trials were well under way. When alendronate was being developed, available animal models failed to mimic with fidelity osteoporosis in postmenopausal women; furthermore, although models showed that the drug could prevent bone loss and strengthen bone biomechanically, they could not predict reliably the human therapeutic dose. Merck researchers created "postmenopausal osteoporosis" in baboons.[18] Baboons walk upright, and like women, female baboons have a 30-day menstrual cycle. "Menopause" was induced surgically by oophorectomy, resulting in rapid bone loss that was reflected in diminished bone mineral density (BMD). On the basis of a 2-year dose-ranging experiment in baboons, 5 mg of alendronate daily, administered orally, was projected to be the human therapeutic dose.

The Alendronate Phase III Osteoporosis Treatment Study,[19] which tested doses of 5, 10, and 20 mg, was under way when data from another study[20] showed that 20 mg daily was more than is necessary to maximally increase BMD. This led to a momentous decision to change doses and design in the middle of a fracture outcomes trial: patients receiving 20 mg daily were switched to 5 mg daily for the remainder of the trial, approximating 3-year dosing of 10 mg daily (the doses in the other groups were not changed).[19] And while both phase 3 fracture trials were ongoing, the Food and Drug Administration (FDA) changed its requirement from a 2-year to a 3-year fracture end point. The FDA made the change because an earlier study of osteoporosis-related fractures involving a different agent, etidronate, showed a significantly lower risk of new vertebral fractures with etidronate than with placebo at the end of year 2. However, by the end of year 3, the treatment effect over the entire 3-year period was lost.[21] The FDA guideline revision created a 1-year delay in the new drug application and illustrates the changeable nature of regulatory requirements.

Fortunately, this phase 3 trial could be modified midcourse. On completion, the trial showed that 10 mg was efficacious and more efficacious than 5 mg in terms of BMD at all skeletal sites, including the femoral neck (Fig. 3).

A second phase 3 trial, the Fracture Intervention Trial (FIT), was in progress at the time of the initial FDA approval of alendronate for the treatment of osteoporosis and was conducted in two parts.[22,23] A component of FIT, the Vertebral Fracture Study of FIT, lasted 3 years and enrolled patients with previous vertebral fracture and low BMD in the hip.[22] The Clinical Fracture Study of FIT tested the effect of alendronate over a period of 4 years on fracture outcomes in postmenopausal women with low BMD but no previous fracture.[23] The initial goal was to compare 5 mg of alendronate daily with placebo; to maintain equipoise, all participants received vitamin D and calcium supplementation.

Hip fractures, the most serious consequence of osteoporosis, are associated with excess mortality of approximately 25% within 1 year; they represent the largest population health issue re-

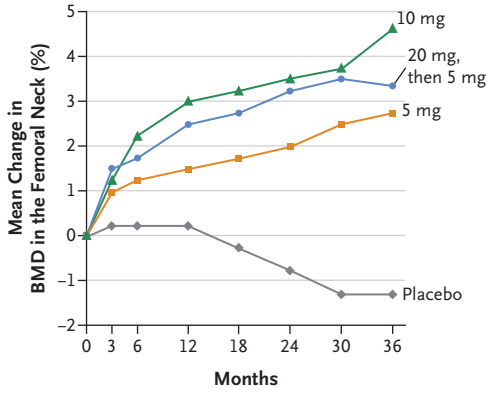

Figure 3. Changes in Bone Mineral Density (BMD) from Baseline in Women with Postmenopausal Osteoporosis.

Patients received daily doses (indicated in figure) of alendronate or placebo for 3 years in a phase 3 trial. While the trial was under way, data from another study showed that 20 mg daily was more than is necessary to maximally increase BMD; therefore, patients who initially received 20 mg daily were switched after 2 years to 5 mg daily (to approximate 3-year dosing of 10 mg daily). Adapted from Liberman et al.[19]

lated to the disease. So when phase 3 data became available, the Merck alendronate team focused on hip BMD. It appeared that 5 mg daily probably would be sufficient to prevent vertebral fractures, but the effectiveness of that dose in preventing nonvertebral fractures was uncertain. With no apparent safety differences between the 5-mg and 10-mg doses, the decision was made 2 years into both FIT studies to switch patients from 5 mg to 10 mg for the remainder of the trials. By completion, the Vertebral Fracture Study showed a 51% lower risk of hip fractures with alendronate than with placebo,[22] and the Clinical Fracture Study showed a 56% lower risk of hip fractures and a 36% lower risk of any clinical fracture with alendronate than with placebo among women who had had baseline osteoporosis at the femoral neck (T score, –2.5 or less).[23] These and other trials provided evidence that led to approval of alendronate in many countries for the prevention and treatment of postmenopausal osteoporosis.

Almost immediately after alendronate was introduced in the United States, Merck was contacted by clinicians from the Mayo Clinic who observed esophageal ulcerations and erosions in women using alendronate. The risk of esophagitis with alendronate was known, but the newly observed lesions were more severe than what had been seen infrequently before. The lesions resulted from "pill" esophagitis — a chemical irritation caused by prolonged contact of bisphosphonate with esophageal mucosa. During the research studies, participants had been carefully instructed to take alendronate with a full glass of water and to remain upright for at least 30 minutes; once out in the "real world," these instructions were not followed closely. Once this issue was clarified by rapid publication of a letter that included images of esophageal ulcerations,[24] a "Dear Doctor" letter in advance of the publication, and strengthened "warnings" and "precautions" sections in the product label, the incidence of this complication decreased. This shows the value of real-world experience to complement information obtained from clinical trials.

Another lesson we learned from the alendronate experience is that animal models, even when they closely mirror human disease, may not afford sufficient correlation and precision to predict the human therapeutic dose.[18] Bone turnover in humans is slower than in rodents, so manifestation of drug effect takes longer in humans. Therefore, the correct human dose was not revealed in the initial phase 2 trials but was confirmed only in the longer phase 3 trials.

FUTURE CHALLENGES

In addition to the challenges of complexity illustrated in the two examples above, chronic diseases pose particular challenges for clinical trials, which explains, in part, the dismal record of success in areas such as Alzheimer's disease (97% failure rate). Once Alzheimer's disease is established, it may not be amenable to intervention; at that point, the underlying pathologic processes may be too advanced. A number of potential biomarkers are now being evaluated in Alzheimer's disease that may make it feasible to perform clinical trials involving patients who are at an early or asymptomatic stage; however, the predictive value of these markers is currently unknown. Although a subgroup of people with clinical Alzheimer's disease can be identified by genetic testing, performing clinical trials involving patients who have defined genetic abnormalities may not be relevant to the broader population. A trial involving patients at a very early stage of disease could take 10 to 15 years to show efficacy. In addition to the practicalities of recruiting and retaining patients over so long a period, the drug patent would expire before regulatory approval could be achieved. If we are to tackle these long-term issues, we need to rethink how we develop such drugs.

Complexity is, in my opinion, the major challenge facing large pharmaceutical companies in conducting clinical outcomes trials. The examples provided illustrate a number of factors that generate complexity, including scale, design, geography, and detection of a rare safety signal in a "noisy" background. The examples also illustrate subsequent challenges, such as translating trial findings into clinical practice. The examples represent successes, but for each success there are many failures that consume time, effort, and resources and also affect morale.

Under the presumption that the proficiency and efficiency of clinical trials are improving, success rates should go up and costs down. Yet the opposite is true, and increasing complexity is a key reason (Table 1).[2,3,25,26] Some ongoing outcomes trials will cost a staggering $500 million

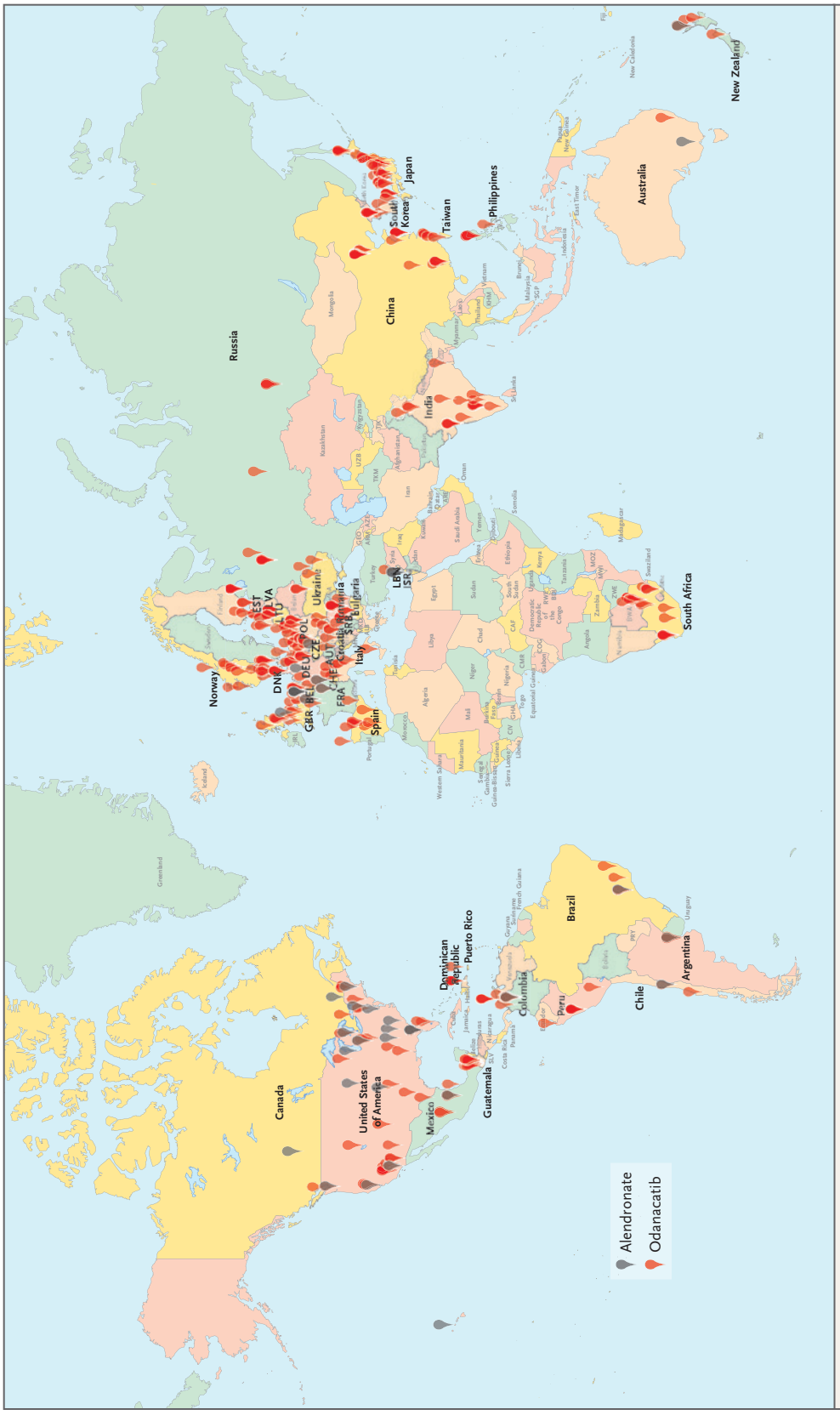

Figure 4. Then and Now — Clinical Outcomes Trials for Osteoporosis.
The figure depicts the expansion in geographic sites (e.g., in Asia and Africa) for phase 3 fracture trials of odanacatib in 2015 as compared with alendronate in the 1990s. Orange markers indicate odanacatib sites (with redder markers indicating multiple sites), and gray markers indicate alendronate sites. AUT denotes Austria, BEL Belgium, CHE Switzerland, CZE Czech Republic, DEU Germany, DNK Denmark, EST Estonia, FRA France, GBR United Kingdom, ISR Israel, LBN Lebanon, LTU Lithuania, LVA Latvia, and POL Poland.

to $1 billion (an investment made without certainty regarding the result).

Further evidence of increasing complexity is apparent in a comparison of the above-described alendronate trials with a recently completed outcomes trial of odanacatib, a new agent that was being evaluated for osteoporosis therapy. The alendronate phase 3 trials (including FIT), conducted in the 1990s, studied approximately 7800 patients at approximately 60 sites in 20 countries. The odanacatib phase 3 outcomes trial, completed in 2015, evaluated approximately 16,000 patients at 387 sites in 40 countries (Fig. 4). In addition, the duration of the double-blind period of the odanacatib (base plus first extension) trial was 5 years versus 3 years for the alendronate trials. The detection of an unexpected safety signal ultimately led to discontinuation of odanacatib development after a 22-year research and development program.

Given the complexity of outcomes trials, it sometimes seems remarkable that they ever succeed; that they do is testimony to the underlying science and the multidisciplinary teams that conduct the trials. In closing, we should keep in mind a dictum often attributed to Einstein, that "Everything should be made as simple as possible, but not simpler."[27]

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