CenterWatch

Compilation Report Series

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Table of Contents

Foreword

I'm pleased to present the fourth report in the Compilation Report Series, the *Regulatory Compilation Report*, which focuses on GCP and methods used to ensure compliance with regulatory requirements that safeguard data integrity and human subject protection in clinical trials.

This report is a comprehensive compilation of archived CenterWatch articles based on in-depth interviews, investigative journalist reporting and original research and analysis.

Topics include:

- The number of warning letters issued to investigators has dropped in recent years, due to improved training and the incorporation of GCP requirements into operations; however, complaints received by the OSI have skyrocketed.
- 'Right to Try' laws, granting terminally ill patients access to investigational drugs, have been purported to make said access easier for patients than the FDA expanded access program. The movement continues to gain momentum as more breakthroughs occur in precision medicines that are targeted to receptors rather than diseases.
- The benefits and burdens of the Physician Payment Sunshine Act has pharmaceutical companies, investigators, sponsors and CROs buzzing as the process, though it has been in place for years, continues to be fraught with challenges and data errors.

For more than 20 years, CenterWatch has had the responsibility and privilege of dedicating its energies to objectively observing the clinical trials industry. CenterWatch has had a unique and unprecedented opportunity to serve as watchdog, educator and curator.

We hope you enjoy reading this *Regulatory Compilation Report* and gaining more insight about the multifaceted regulatory process as much as we have enjoyed the opportunity to report on it.

Joan A. Chambers
Chief Operating Officer

FDA warning letters drop as audit preparation increases

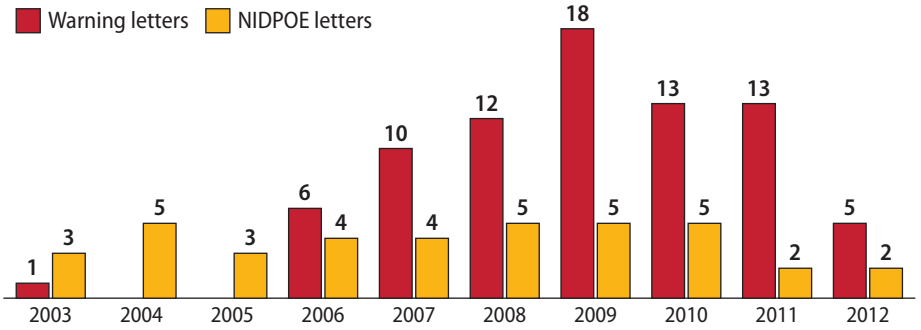
Sites boost training, GCP compliance, incorporation into their operations

Warning letters issued to investigators by the FDA's Center for Drug Evaluation and Research (CDER) have dropped 13% (annualized) during the past five years as the industry has strengthened efforts to ensure sites comply with regulatory requirements that safeguard data integrity and human subject protection in clinical trials.

Overall, warning letters related to Good Clinical Practice (GCP) violations issued during the past five years to sponsors, CROs, IRBs, investigative sites and two other areas inspected by CDER—Good Laboratory Practice and bioequivalence—have decreased nearly 4%.

The drop in warning letters to clinical investigators is unrelated to government spending cuts; FDA spokesperson Tara Goodin said the number of investigators for CDER-related inspections has not been reduced. Instead, several other factors likely have contributed to the decrease. During the past five years, clinical sites have improved their on-the-job training and have improved efforts to incorporate GCP requirements into operations. Investigators have become better informed about their responsibilities in complying with GCP requirements. FDA metrics also suggest sites can effectively correct violations before they result in a warning letter. Last year, 40% of investigators were asked to voluntarily correct violations identified in an FDA inspection; all but 3% were able to comply with the law and avoid official action.

OSI warning and NIDPOE letters



Note: NIDPOE = Notice of Initiation of Disqualification Proceeding and Opportunity to Explain

Source: FDA Office of Scientific Investigations

Sponsors also have focused on GCP compliance. Many large companies have begun internal clinical quality departments, conducting their own site audits and preparing sites for FDA inspections. Sponsors also are more likely to follow up on problems identified during inspections and make sure non-compliant sites actually correct the problems.

"Sponsors are looking for compliance with GCP not just to avoid a warning letter, but the bigger issue is that if the FDA invalidates the site, it messes up the trial," said Matthew Weinberg, CEO of the Washington, D.C.-based Weinberg Group, a consultancy focused on regulatory strategies for sponsors. "That is the single largest concern. You don't want bad data. You don't want a site that had good patients being invalidated for bad practices."

Complaints on the rise

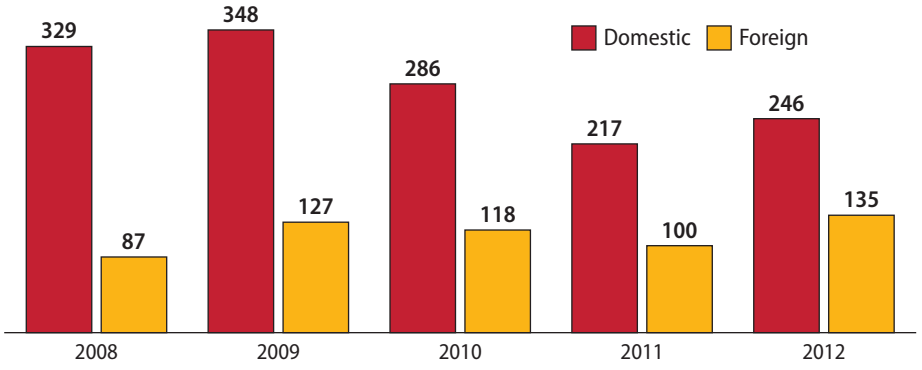
While the number of GCP-related warning letters has decreased during the past five years, the number of complaints received by the Office of Scientific Investigation (OSI), the CDER division responsible for verifying the integrity of safety data and ensuring protection of human research subjects, has surged 150%, from 241 in 2008 to 603 last year. After the tragic deaths of two clinical trial volunteers more than 10 years ago, the FDA made it easier for the public to anonymously report any questionable behavior from investigators or site personnel by phone or the internet. As a result, the number of complaints for GCP-related violations has nearly tripled in the past decade.

According to FDA metrics, only about one quarter of complaints received about investigator non-compliance during the past five years re-

sulted in an investigation. For clinical investigators, 82% of inspections conducted in 2012 were for data audits, while only 18% were in response to complaints. In addition, the vast majority of investigator inspections last year resulted in either no action taken against the site (57%) or voluntary action (40%) to correct a problem.

"There is a difference between a complaint and a valid GCP issue that can be cited on a warning letter," said Mark Lacy, CEO of CORE and Benchmark Research. "Since the advent of the World Wide Web and the speed and ease of communication continually improved, the internet has made it much easier for anyone to file a complaint, many of which are unfounded."

Foreign and domestic clinical investigator inspections conducted by OSI



Source: FDA Office of Scientific Investigations (CDER 2008-2012)

Most inspections at sites

Investigative sites are the most critical part of the GCP process, since they are responsible for a majority of clinical trial conduct, including data collection and patient consent. As a result, more investigators are inspected than sponsors, CROs or IRBs.

CDER's on-site GCP inspections are conducted to evaluate the quality and integrity of data submitted to the agency in support of new product approvals and to ensure research participants are adequately protected. In 2012, 53% of CDER's GCP-related inspections were conducted at sites.

"A risk-based approach to oversight leads to more inspections of clinical investigators than other types of inspected entities," said the FDA's Goodin.

The three most frequent investigator violations identified in FDA inspections haven't changed over the past five years. The top problem area remains investigators who do not ensure site personnel follow the investigational plan—the number of warnings issued for this violation doubled during the past five years. Other common infractions include failure to maintain accurate case histories and improperly obtaining informed consent from research participants.

Lacy said sites often struggle with compliance because they rely on Clinical Research Associates (CRAs)—who monitor study data for the sponsor—as their quality control agent instead of establishing internal oversight.

"Sites should be establishing a robust quality control program that allows mistakes to be identified in real time," he said. "Then they need to track these trends and install corrective action plans that will prevent these issues from repeating in the future. Currently, only the largest and most professional research companies can afford the monetary and human resource cost of such programs."

Laurie Halloran, president and CEO of Massachusetts-based Halloran Consulting Group, said the top problem areas identified by FDA inspections indicate investigators don't understand the importance of applying GCP in their day-to-day activities.

"It is tremendously difficult for busy physicians and nurses to balance the needs of patients with the demands of a study," she said. "GCP is always an interpretation that has to be applied on top of what is occurring as part of patient treatment. Sometimes in order to follow the protocol to the letter, a patient cannot be a subject. Warnings are always issued when there are systematic violations, and those usually occur when the basics are not able to be infused in everyday activities."

IRBs struggle with compliance

IRBs represented 12% of GCP-related inspections conducted by CDER last year. Over the past five years, CDER has inspected an average of 93 IRBs each year. In 2012, the majority of inspections resulted in either no action against the IRB (50%) or voluntary action (42%).

Significantly, out of the 18 CDER warning letters issued to IRBs during the past five years, all but two of the recipients were institution-based IRBs.

Felix Khin-Maung-Gyi, PharmD., CEO of Chesapeake IRB, said these institutions often are not well-equipped to provide IRB oversight. "They may conduct a low volume of research annually and they don't have that type of experience that high-

volume research institutions or independent IRBs have with regard to IRB regulations. That, combined with not understanding changes in interpretations of regulations or standards of practice, makes them more likely to be noncompliant," he said.

The most frequent IRB warnings include failing to record enough detail in meeting minutes to indicate actions taken by the IRB, follow written procedures for research or maintain adequate documentation of IRB activities.

Stuart Horowitz, Ph.D., president of global professional services at WIRB-Copernicus Group, leads the company's consulting arm, which provides support services for human research protection and ethical research programs, along with other aspects of clinical research, for institutions, sponsors and CROs. He sees many IRBs struggle with compliance issues because they lack written procedures or have procedures without easy-to-follow instructions—many IRB procedures reviewed by the consulting group are a collection of policies and regulatory excerpts that fail to describe how they should be carried out. In addition, the use of checklists, which could help avoid mistakes, and electronic software tools are uncommon at most IRBs.

"Most IRBs are still working without IRB software," said Horowitz. "Some are paper-based. It's not unusual to have some combination of homemade database, spreadsheet, email, Word documents and PDF files. It turns out there is a family of electronic solutions on the market that can really help."

Horowitz said many IRBs and the people who lead them surprisingly have trouble with basic details about IRB administration. More than one-third (34%) of warnings issued to IRBs last year involved a failure to record enough detail in meeting minutes to show what actions were taken. For example, he said, many organizations struggle with recording the total number of votes taken in a meeting and how that relates to the quorum; they don't know how to track who arrives late to the meeting or leaves early or which member abstains from a vote. The FDA wants the minutes to record the names of the people who voted on a protocol but when they review this information, investigators often find the number of board members at the meeting doesn't match the number of votes recorded. "It isn't rocket science, but it's easy to make mistakes," he said.

Meanwhile, the proportion of GCP-related inspections at sponsors and CROs increased nearly 19% (annualized) during the past five years. Sponsors and CROs comprised 8% of CDER's GCP-related inspections last year. Since 2010, when the FDA issued four GCP-related warning letters to sponsors as part of a more aggressive approach to enforcing regulations, CDER has not issued any GCP-related warning letters to sponsors or CROs.

Michael Swit, special counsel in the FDA law practice at California-based law firm Duane Morris, said the role of sponsors in GCP compliance should not be underestimated. Sponsors, he said, have obligations to oversee studies and ensure GCP regulations are followed.

"Obviously the sponsor also has a great interest in that it wants the data to be valid," he said.

2012 OSI inspection-identified clinical investigator deficiencies

	Domestic sites	Foreign sites	All sites receiving an 'official action'*
Protocol violations	38%	26%	78%
Poor recordkeeping	26%	21%	56%
Poor drug accountability	9%	2%	33%
Informed consent violations	7%	8%	44%
Poor communication with the IRB	4%	3%	22%
Poor adverse event reporting	1%	3%	N/A

*22% of all site inspections resulting in an OAI designation were due to submission of false data

Source: FDA Office of Scientific Investigations

Audit preparation on the rise

Efforts to educate investigators and site personnel about GCP requirements and prepare for FDA inspections has increased since 2009, when the number of warning letters issued to investigators spiked 33% from the previous year. The FDA's Goodin said it's difficult to identify the cause of warning letter fluctuations or draw significant correlations for a variety of reasons, including the small sample size, and cautioned against reading too much into the numbers. Yet the sudden rise in warning letters was taken seriously and efforts to improve GCP compliance increased.

At PMG Research, an integrated site network based in North Carolina, for example, preparation for FDA inspections begins with training staff members on standard operating procedures and core practices developed by the company. An internal audit group then inspects each site every quarter to monitor compliance with these procedures.

"We are keeping the pulse of

what is going on. Are there people who need additional training? Are there studies where things are going wrong? We look at what is going on and what we need in terms of corrective action," said Yvonne McCracken, director of business development at PMG. "There is more focus on being prepared. All of our sites are audit ready because of our CAPA (corrective action and preventive action) program; more and more sites are using that as a marketing tool. The larger sites, and even some of the smaller ones, are making sure they have that internal audit piece in place so things are where they should be."

Sponsors and CROs also ready sites for FDA inspections by reviewing documents to identify areas that might need an explanation for inspectors and advising staff how to mentally prepare for the review.

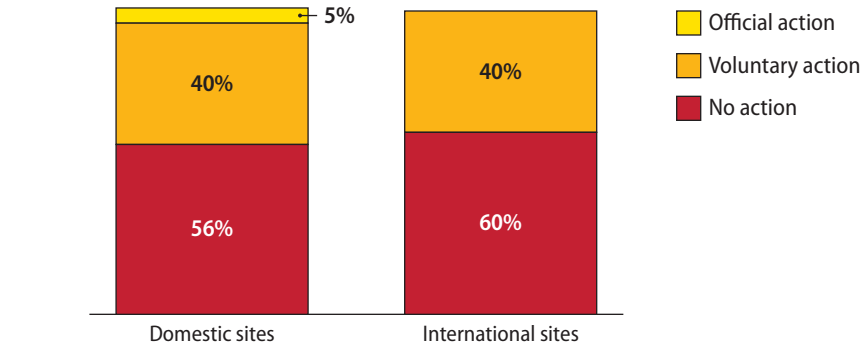
The Weinberg Group includes a compliance group that performs independent GCP audits of clinical trials for biopharmaceutical companies. The group has seen an increase in the number of internal audits in advance of FDA inspections.

"We are hired, in essence, to find the problems before the agency does, so they can be logically and correctly addressed before the agency comes to the site. No one is fudging the data, but there are issues you could fix before the inspection," said Weinberg. "Sponsors are focused on the risks inherent in the GCP process and are doing what they need to do to make sure there is less risk."

In addition, there is a growing interest in formal training and certification programs for both Clinical Research Coordinators (CRCs) and Principal Investigators (PIs). The Association of Clinical Research Professionals (ACRP) and the Society of Clinical Research Associates (SoCRA) both offer certification programs. The industry also has seen an increase in the number of GCP training programs offered by private companies, CROs and industry organizations.

"The role of the research site has matured quite a bit in the last five years, and it's likely that between the education and certification initiatives and just the general experience level of research site personnel, the wisdom of experience has improved GCP compliance," said Halloran. "Given that the most common inspectional findings have not really changed in decades, in my opinion, the sites that are noncompliant are still that way, but it's likely there are just fewer of them."

2012 OSI inspection results



Source: FDA Office of Scientific Investigations; N=183 domestic and 116 foreign site inspections

GCP under risk-based monitoring

As the industry moves toward risk-based monitoring, a model that monitors trials electronically and sends monitors to sites only when necessary rather than every four to six weeks, many have begun to question how this approach will affect site responsibility for GCP compliance, and whether the ability to detect questionable behaviors at sites will significantly change.

Dan White, vice president of global operations at Quintiles, said FDA and EMA guidance documents on risk-based monitoring don't change the regulatory requirements specific to the investigator or sponsor/monitor. Sites will continue to be accountable for medical oversight, protocol adherence and GCP compliance. Yet White said the concept of risk-based monitoring is built on the premise that sponsors/monitors can identify risks prospectively and use systems to give early insights into data quality and study integrity, two direct causes for warning letters.

"When executed well, risk-based monitoring will reduce the issuance of warning letters," White said. "Risk-based monitoring gives the sponsor or monitor the ability to respond more quickly to signals of issues, and mitigate."

Many investigators, however, believe risk-based monitoring will increase their workload, since many activities routinely performed by monitors—such as source document review—will be transferred to site staff. In addition, while sites will shoulder more of the burden for data quality, fewer monitors will visit the sites as liaisons to the investigators and study coordinators. As on-site oversight diminishes, many believe complaints and GCP deviations will rise.

"This will be a challenge for sites,

from a manpower and cost standpoint," said Lacy. "The sites/PI already are held responsible for the conduct of the trial during the FDA inspection process. This is not to say that the FDA does not assess the level and quality of the monitoring, but a site/PI does not receive a warning letter because the monitoring was inadequate. They receive this warning letter based upon non-compliance issues related to the conduct of the study."

Looking ahead

The steady growth in GCP-related complaints suggests the industry may be focusing on the wrong areas to improve the compliance burden. The industry has increased emphasis on GCP-related training and accreditation, yet these efforts have not reversed the steady growth in the number of complaints for GCP-related violations during the past decade. In particular, protocol violations have doubled in the past five years and remain the top area of non-compliance for investigators. Rather than focus on more training, leaders believe the industry needs to look at why sites are violating protocols, and how study design creates some of these problems.

In addition, some believe the focus on GCP training illustrates how sponsors and CROs tend to approach the management of sites as a way to reduce the likelihood of failure, when it would be more valuable to build relationships with investigators and give sites the support they need.

"A more balanced approach is definitely needed," said Lacy. "GCP training is important, but it is not the answer to all issues that occur during the course of a trial. There should be more focus on collaborative partnerships. Very often it seems as if the sponsor is working within a silo when developing protocols. It would be more efficient if it were to engage with clinical sites during this process, which would result in the partnership being more effective."

IRB market consolidating rapidly

Private equity driving a new commercial ethical review landscape

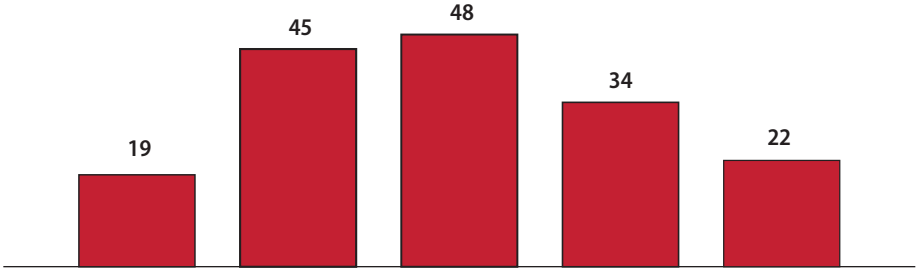
The commercial Institutional Review Board (IRB) landscape, historically dominated by small, owner-operated companies, has begun to rapidly consolidate over the past two years, signaling a different environment for ethical review and oversight of human subject projection in clinical trials going forward.

This marketplace, which now has about three dozen commercial IRBs, is widely expected to continue consolidating until only four or five major players are left.

Consolidation has been driven by the need for more economic efficiency in the review of research protocols and related materials, such as informed consent documents, to ensure the safety of human subjects in clinical trials. Regulatory demands on IRBs have increased, and studies have become more complex. Commercial IRBs also are merging to create economies of scale for providing more effective and streamlined oversight, as the industry moves toward central review models for multicenter trials.

"Bigger, private IRBs want to get rid of competitors who sometimes are taking away their business—particularly business from the pharmaceutical industry," said Arthur Caplan, Ph.D., head of the Division of Medical Ethics at New York University Langone Medical Center in New York, N.Y. "Some of it is just economy of scale. The big guys often are just more efficient. They can undercut the little guys in terms of price, they can do better quality control, they have better speed and they have the money to basically buy the small ones."

Number of commercial IRBs operating in the U.S.



Source: CenterWatch

While most sponsors and investigative sites haven't paid close attention to consolidation in the IRB landscape, much of which has been backed by private equity firms, the movement could have a profound impact on human subject protection review and oversight in the near future.

The effects of M&As

Mergers and acquisitions backed by private equity have significantly altered the commercial IRB landscape over the past two years. Nearly all commercial IRBs—also called independent IRBs—began as mom-and-pop companies in the 1980s or 1990s, with the landscape remaining highly fragmented and immature for the past three decades. Now, deals have begun to consolidate this landscape and allow companies to scale up and meet the growing demand for more efficient, higher quality ethical review services.

Two dominant players have emerged from the recent wave of acquisitions. The first formed when two of the largest IRBs—Western Institutional Review Board (WIRB) and Copernicus Group Institutional Review Board—were acquired by Arsenal Capital Partners in 2012 and combined to form the WIRB-Copernicus Group (WCG), although each IRB continues to operate separately. In June, two additional IRBs—Aspire IRB, located near San Diego, and Kansas City, Mo.-based Midlands IRB—joined WCG, expanding the group's presence in two major clinical research hubs. WCG also formed a new cancer-focused IRB, WCG Oncology, in June.

The second emerged last year when Chesapeake IRB, a 20-year-old, privately owned, commercial IRB, sold a majority stake to private equity firm Audax Group; Chesapeake IRB then

acquired Goodwyn IRB and Canada-based IRB Services in March and April.

Greg Koski, M.D., Ph.D., former director of the Office for Human Research Protections at the U.S. Department of Health and Human Services, said the private equity-backed acquisitions signal a change in community attitudes about IRBs, shifting the focus toward the need for IRBs to run like businesses and generate profits. Arsenal's acquisitions of WIRB and Copernicus Group, for example, were part of a broader strategy to provide a new generation of services to the clinical trials enterprise. WCG has expanded to include IRBNet, which provides research compliance software for institutions, and created the WCG Academy to train site staff on specific protocols using online tools.

"IRBs always have been a business, to a certain extent, but these are major investment capital groups looking at IRBs as an investment, which I think is an intriguing sort of development. Who would have ever thought that ethical review would be an investment for a venture capital group?" said Koski, who is president and co-founder of the Alliance for Clinical Research Excellence and Safety (ACRES). "I'm not making a value judgment on whether or not that is a good thing. I'm simply saying that's the way it is."

Cami Gearhart, CEO of Quorum Review IRB, sees the independent, standalone IRB landscape changing. After a private equity firm acquires a commercial IRB, she said, the investors usually need to increase their value—typically in three to five years—and start "rolling up" companies.

"This is a space that is of great interest to the equity investors," said Gearhart. "My prediction is that in five years, the IRBs that currently are owned by equity investors are going to be small components, or relatively small components, in these larger organizations that offer a variety of services and products."

Recent IRB mergers & acquisitions

Date	Transaction
December 2011	Schulman Associates IRB acquires Independent IRB
March 2012	Arsenal Capital acquires WIRB
June 2012	Arsenal Capital acquires Copernicus Group IRB
December 2012	Arsenal Capital acquires IRBNet
May 2013	Audax Group acquires majority stake of Chesapeake IRB
March 2014	Chesapeake IRB acquires Goodwyn IRB
April 2014	Chesapeake IRB acquires IRB Services
June 2014	Aspire IRB, Midlands IRB acquired by Arsenal Capital

Source: CenterWatch

During the past decade, the IRB landscape also has consolidated through other mergers, such as Shulman Associates IRB acquiring Independent IRB, and has seen some small IRBs go out of business. CenterWatch analysis shows the number of commercial IRBs in the U.S. has dropped from 45 in 2002 to 34 in 2012, a 25% decline.

Consolidation can give IRBs economies of scale that allow them to implement more efficient processes and technologies for streamlining and improving ethical review processes. An Association for the Accreditation of Human Research Protection Programs (AAHRPP) study found staff workload at IRBs has increased nearly 90% in recent years. Commercial IRBs are using capital to add resources that allow them to meet demands from regulators and accrediting organizations to perform to higher standards. In addition, as protocols become more complex and ethical review expands into new scientific areas, large IRBs are adding experts qualified in a wide range of areas to review studies.

"As there is more research on personalized medicine, cancer and orphan drugs, the IRBs have to acquire those skill sets to review them," said Caplan, who also is a member of an advisory board to WCG. "I do think the IRB world is expanding to include not just human subjects, but also engineering viruses, for example, and experiments that might involve animals or microbes. Biosafety may well fall to the private IRB world to review."

There also has been growing acceptance from both regulators and industry for different models of central review that allow a single, central IRB to oversee U.S. multi-site trials, rather than have dozens of IRBs separately review and approve documents at each site. Central reviews, which can reduce duplication of effort and delays, require large IRBs with experience to handle them.

"Running a trial with 50 sites or 80 sites each served by its own separate IRB on its own timeline and with its own preference for language and informed consent is a highly, highly fragmented world that drug companies can no longer afford," said Donald Deieso, Ph.D., WCG's chairman and CEO. "They can't afford to wait six to eight months to get a study started. They can't afford to have the inefficiencies, as the older, or more traditional, approach would have dictated."

A few major commercial IRBs, such as Quorum Review IRB, have been able to maintain themselves as family-owned businesses despite receiving frequent calls from private equity investors interested in new acquisitions. Yet market trends—including a decline in the number of trials conducted in North America—and demands for more significant investments in technology have made it increasingly difficult for smaller IRBs to compete.

"It's a tough market. We are losing the smaller IRBs," said Quorum's Gearhart. "It's becoming more and more difficult for small IRBs to compete or even for a small IRB to get started as a standalone."

Some smaller IRBs have joined alliances, such as the Consortium of Independent Review Boards (CIRB), to share infrastructure and develop "best of breed" policies and procedures that provide economies of scale. In addition, some smaller companies are staying in business by developing certain niches, such as expertise in medical device trials or phase I work, or by delivering better customer service to sponsors and CROs than larger companies can provide.

"One of the advantages of the little IRBs is that they have fewer clients, so they can spend more time with their clients and often can turn things around more quickly," said Marjorie Speers, Ph.D., who recently retired from her position as president and CEO of the AAHRPP, which she had led since its founding in 2001. Speers now owns Speers Research Strategies.

"The bigger IRBs need to provide the same customer service," she said. "If that happens, I think it's going to be very difficult for a little IRB to compete."

The consensus among industry watchers is that small IRBs are likely acquisition targets or eventually will be so small they won't be able to compete in the space. In May, the FDA issued a final guidance on how an approved study should be transferred between IRBs without disrupting the clinical trial, which suggests the agency expects more IRBs to consolidate or shut their doors.

"There will be more consolidation going forward," said Deieso. "The market is demanding performance and the expectations are increasing such that the smaller companies simply cannot conform or comply. The ones that are going to survive need to have the financial wherewithal to make the investments and advance technology delivery systems."

Profiles of two organizations driving consolidation

	Arsenal Capital Partners	Audax Group
Year founded	2000	1999
Offices	New York, Shanghai	Boston, New York, Menlo Park (CA)
Assets under management	$1.7 billion	$5 billion
Sector focus	Specialty industrial; Healthcare	Business and consumer services; Energy; Healthcare; Media; Technology; Telecommunications

Source: CenterWatch

A new landscape

The larger, commercial IRBs look at M&As as a way to professionalize the field and increase the quality of human subject protection. When Coast IRB was dissolved several years ago after the Government Accountability Office (GAO) submitted a fake clinical trial application the IRB approved, it raised questions about the integrity of all commercial IRBs.

"The bigger, independent IRBs recognize that if there is a weak one among them, it hurts all of them," said Speers.

Felix A. Khin-Maung-Gyi, Pharm.D., founder and CEO of Chesapeake IRB, said AAHRPP accreditation has provided a mechanism to identify IRBs that are committed to quality and excellence. However, he said achieving and maintaining accreditation requires the ongoing dedication of people and dollar resources, which can be difficult for small, independent IRBs.

"Sponsors realize that the experience they may have had with a small, independent IRB for one therapeutic area may not provide a sustainable model for a study with a larger number of sites either in the same or different therapeutic area, because the structure or support needed to provide quality and timely services is not there," said Gyi. "I find it difficult to find a clear view to seeing how a small, independent IRB without appropriate resources can find economies of scale in the marketplace to successfully provide the regulatory mandated goal of assuring human research protections."

Speers believes IRB consolidation, in the end, will lead to better subject protection since sponsors, who are asking for higher quality in reviews and more clinical content, will demand that the remaining IRBs have the appropriate expertise to review protocols. Also, with only a handful of companies left, sponsors and regulators will monitor those IRBs carefully.

"They are not going to be able to cut corners. They are going to have to perform at a high level," she said.

Sponsors and CROs typically want

to work with three or four IRBs, so that if one review board has a problem or doesn't perform, they have other IRBs they can engage. Yet, if consolidation results in higher IRB standards and more reliable oversight, Speers said the ultimate impact on sponsors will be positive.

"Sponsors have so many things they have to deal with in a study. If they could be assured if they use IRB 'X' and IRB 'X' is performing well, that is one less thing they have to worry about," she said. "So if there are fewer IRBs, it becomes easier for them to engage those IRBs."

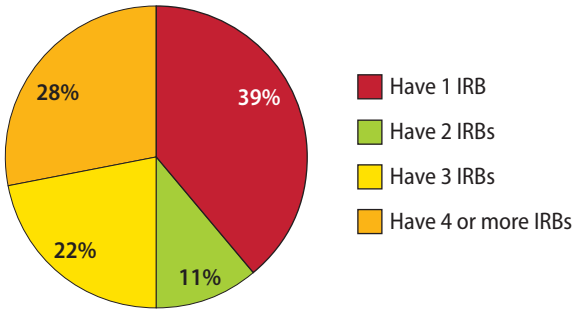
As the industry moves toward central review models for multi-center studies, most agree having a single, large IRB review all unanticipated problems, adverse events and protocol changes at multiple sites in a study gives the board a more complete picture of the trial and will lead to more consistent oversight and better subject protection.

"In multi-center studies, it is a disservice to the research subject to have a disconnect in the type of review and continuing oversight provided at one site versus another. The benefit to the subject, and collaterally onto the sponsors and investigators, is a consistency of review," said Gyi. "That is why the different central review models have started to emerge."

For their part, sites will have fewer choices in terms of which IRBs they work with on a clinical trial. IRBs, which will be held to higher standards by sponsors and regulators, are expected to more heavily scrutinize conduct at sites. Yet Speers believes working with a smaller number of IRBs can be advantageous for sites, since there will be more consistency in requirements.

"Right now, IRBs all have to follow the regulations, but their procedures and forms can vary, such as what they want reported or not reported," said Speers. "The site has to figure that out for every single IRB it uses. If it didn't have to figure that out 20 times—but only five or 10 times—that is going to be a lot easier."

Institutional Review Boards in academic settings



Source: AAHRPP 2012; N=183 academic institutions

IRB consolidation does, however, have disadvantages for sponsors and CROs. Large IRBs may not be able to provide the same level of service that smaller IRBs can offer in terms of turning a study around quickly, specializing in a particular area of research or providing good customer service. As large IRBs automate processes and interactions to increase efficiencies, it will become harder for them to offer local, individualized attention to study- and site-specific human subject projection needs.

"One of the drivers for equity investors is to increase efficiency. The smaller IRBs can tailor their services to their one or two big clients. In the future, there is going to be more pressure to standardize. It will be more difficult for researchers and pharmaceutical companies to receive specialized services," said Quorum's Gearhart. "I think what sponsors and sites will lose as IRBs consolidate is having an IRB that is willing to tailor services to the customer without extra charges."

Questions also have been raised about whether central IRBs can perform reviews that take into consideration local cultural needs, considered essential for a comprehensive ethical review of a clinical trial. Much has been written about the importance of the local IRB in understanding and appreciating the social environment of the site and the patients who will be enrolled in the clinical trial. Some fear the local context won't be evaluated adequately with a central review model.

Lack of competition

As the landscape consolidates, leaving fewer IRBs to compete on price, one of the biggest concerns is that a few market leaders could set pricing and drive up rates more quickly. In the absence of competition, many expect there will be more standardization of services offered and prices charged for those services.

"Certainly the equity investors are smart business people. We already see them looking at novel ways of pricing," said Gearhart. "I think we will continue to see innovation in how pricing is set."

Deieso said there are more than enough IRB opportunities for sponsors to have competitive pricing and for the marketplace to determine prices. But, he noted, sponsors are asking for a higher quality of reviews and more clinical content, which could affect the cost of services going forward.

"We could not be further from a monopoly. Having said that, I think our customers are asking for more. I think they are asking for higher quality. I think they are asking us to rise to higher standards," he said. "With respect to the value delivered and the value that we command in our pricing, those two are connected. I think the industry will respond just as any one of us would pay more for a quality car or a better product on the shelf."

One disadvantage of price increases, according to Speers, would be to discourage hospitals or academic institutions from outsourcing work to commercial IRBs. Commercial IRBs market themselves as conducting faster approvals than institution-based boards. As commercial IRBs achieve scale, they become an even more viable option to take over work from institutional IRBs, particularly as many institutional IRBs are increasingly strapped in terms of capacity. Yet in order for that to happen, Speers said review and study oversight must be priced in a way institutions can afford.

"If there are fewer IRBs, prices might go up. I hope that doesn't happen," Speers said. "If they would like more hospitals to use them, or if they would like to have academic institutions use them for review of research that is not clinical, then they are going to have to pay attention to the pricing."

Concerns also have been raised about the independent IRB landscape consolidating to the point where there is no competition.

"That would not be good. You might even see Washington step in and say you don't have a competitive environment if there is too much consolidation," said Caplan. "The same sort of thing you see in the telecommunications business could happen on a smaller scale to the IRB business. But most of the small guys are not going to be efficient enough to do the work at reasonable prices and do it effectively and efficiently. So I think that trend is inevitable."

Koski said it would be unfortunate for one IRB to gain a monopoly, particularly a for-profit company. He would prefer to see the development of a network that included multiple human research subject protection programs in a pre-competitive space.

"We don't really understand yet all of the forces driving this change, so we are going to have to keep an eye on it as it develops," he said.

Looking ahead

Ultimately, consolidation of commercial IRBs is expected to result in a better, stronger system to protect human subjects in clinical trials. IRBs will need to function at high levels, as increased scrutiny from both industry and the regulatory sector focuses on the few remaining players. Large IRBs, backed by private equity funds, will invest in processes and technologies that can improve efficiencies. These larger companies also must respond to sponsor demands for higher quality reviews, with more clinical content, performed by therapeutic experts.

In addition, as the industry shifts to central review models that can improve the efficiency and consistency of oversight, consolidation will give IRBs the scale to oversee large, multi-site trials.

"Consolidation is long overdue. I'm glad it's happening," said Speers. "I hope the independent IRBs will do it in such a way that it's profitable for them, but that they are aware of the costs and what the market can bear."

All eyes on EMA's adaptive licensing pilot

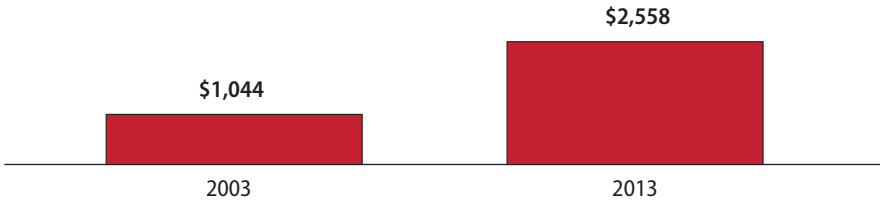
Sponsors could offer innovative drugs to patients 8 years sooner

The industry is closely watching the European Medicines Agency's (EMA) experiment in adaptive licensing, which challenges the way new medicines are evaluated and approved—since a successful outcome could play an important role in moving the approach forward in the U.S. and other regions.

Adaptive licensing, also known as "staggered approval," begins with early authorization of a drug candidate for a small, well-defined group of patients in which the drug's benefits have been clearly shown to outweigh its risks. The approval is gradually expanded into new populations, in an adaptive fashion, as more safety and efficacy data is gathered through clinical trials and real-world outcomes in treated patients. Data about benefits and risks continues to be evaluated during the entire life span of the drug.

The approach could allow sponsors to make innovative medicines available to patients up to eight years earlier than possible under conventional drug development pathways, according to researchers at the Massachusetts Institute of Technology (MIT). It also enables drug developers to collect revenue and real-market experience while they continue to gather clinical evidence about the medicine's benefits and risks. Adaptive licensing also allows for earlier input from regulators and other stakeholders, including prescribers and payers, to inform development strategies that could help reduce costs as well as the risk of late-stage attrition.

The cost to develop an approved new drug has more than doubled
$U.S. millions expressed in 2013 dollars



Source: CenterWatch

"It is the most substantial paradigm shift in regulatory sciences we have seen for the last decade," said Detlef Niese, M.D., an industry veteran who has been involved in discussing the emerging adaptive licensing model with regulators. After having worked for more than 20 years in development at Novartis, Niese now is an independent consultant with Germany-based Dr. Niese Health Science & Policy. "It is a very important effort, on one hand, to make drug development more efficient but, above all, to provide patients early access to new promising treatments as soon as it is responsibly possible."

The outcome of the EMA's pilot program, which began last March and is about to move into its second stage, could give other agencies important information regarding the benefits and limitations of the model and help determine whether it has the potential ultimately to replace the current development and authorization processes for many new products.

Already there have been calls for Congress and the FDA to consider a similar pilot project in the U.S., as industry supports alternatives to the traditional three-phase clinical trial model that could improve efficiency and lower the costs of drug development.

"Every regulatory agency around the world is constantly looking at how it can do its mandate better," said Jeffrey Spaeder, M.D., chief medical and scientific officer at Quintiles. "This pilot project is going to provide other regulators—not only in Europe, but elsewhere around the world—some insights. If it's a success—and there is reason to believe it will be successful—it can't help but impact their calculus in terms of how they follow their mandate in the future. Whether they decide to adopt everything the EMA does or parts of it, it's likely that it will influence the perspective of other regulators."

Alternative pathway tested

The concept of accelerated approvals has been around for years under

different names. The U.S. has Fast Track and Breakthrough Therapy designations, for example, while Europe has a conditional marketing approval program. Last March, the U.K. launched an Early Access to Medicines Scheme. The programs all have a similar aim of trying to speed up the development process, mostly in the area of serious, life-threatening diseases, to allow patients early access to innovative medicines while at the same time protecting safety and maintaining high scientific rigor.

The EMA's pilot project, which builds on earlier work with MIT's Center for Biomedical Innovation, will explore the adaptive licensing approach with medicines in the early stages of clinical development and is particularly relevant for drugs with the potential to treat serious conditions for which there is an unmet medical need. The approach isn't suitable for all trials. Yet one aim of the pilot project is to help develop an understanding of how future adaptive licensing pathways might be designed for different types of products and indications.

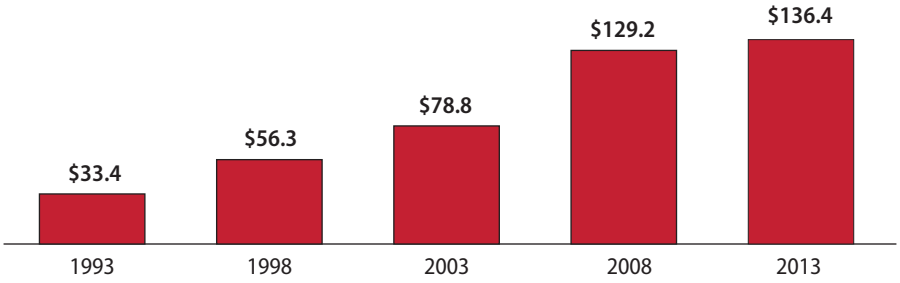
"The idea is to move this into the general drug development paradigm," said Niese. "It's no longer just about serious, life-threatening disease. It's about the development process."

As of late November, the EMA had received 34 applications and assessed 29 as part of its pilot project; nine projects have been selected to move forward to the second stage, which will begin in March with in-depth, face-to-face meetings with sponsors. Companies have until the end of February to submit applications.

The pilot program uses regulatory processes already in place within the existing European Union legal framework, but it requires a radically different approach from the current binary approved/unapproved designation for a drug. Adaptive licensing is based on the idea that knowledge of drugs continues to evolve over time; it allows some drugs to be approved initially for limited populations before being approved for wider use based on clinical evidence.

Total global R&D spending

$U.S. billions



Source: EvaluatePharma

"The current standard pathway to market access is not optimized to enable timely, well-informed patient access to drugs in this kind of niche," said Michael George, M.D., vice president, global therapeutic area head at Covance. "Drug development is very expensive, it takes a long time and there are delays to market access—particularly in those areas where there is high unmet medical need or alternative therapies that really aren't very effective."

Importantly, adaptive licensing requires early collaboration between the sponsor and a wide range of stakeholders who influence patient access to medicines. These groups include regulators, payers, patient and consumer groups, health technology assessment (HTA) bodies, organizations that issue treatment guidelines, healthcare providers and the research community. The process creates a mechanism, called safe harbor, which allows companies to seek early buy-in and guidance from these stakeholders to advance the development of promising drugs. Relevant stakeholders agree on a comprehensive development and licensing plan for each product before it receives an initial approval for limited subpopulations.

"They are looking for strengths and weaknesses of the options for development and the pathway for licensing," said George.

Adaptive licensing could reduce the overall cost of development by allowing better-informed decisions on product viability to be made earlier in the development process. In some cases, it could reduce the time to full-market approval. The concept allows sponsors to receive guidance from regulators and other stakeholders about designing studies that could not only help control cost, but also increase information and insight about the drug. Sharing risk between payers and developers by allowing patients early access to a drug candidate also gives sponsors an early source of revenue while they continue to develop the product.

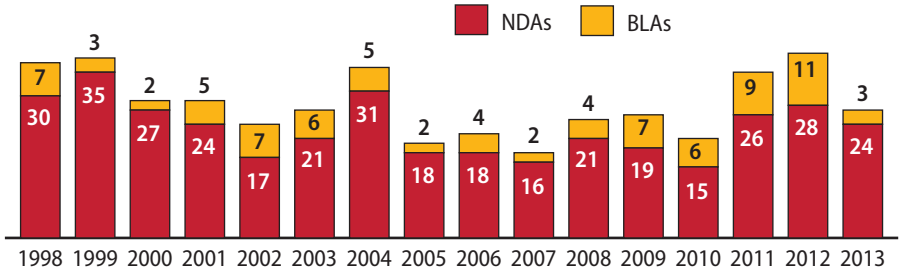
Requiring the alignment of stakeholders early on also could help prevent situations in which a drug completes all stages of review and receives market approval, yet payers are unwilling to cover it because they consider the evidence insufficient to justify the cost. Incorporating reimbursement and market access discussions as part of the adaptive licensing process will be critical to the pilot project's success.

"In the specific context of adaptive licensing, there definitely is emphasis on a collaborative approach between

EMA and the reimbursement authorities," said Pinar Akpinar, Ph.D., senior director of pricing and market access at Icon. "There sometimes is a divide between what is appropriate for regulatory approval versus what some of the countries are looking for in how they define value of the product. In this particular case, it will very much depend on the disease area, the level of unmet need and the level of evidence to be generated."

Annual NME approvals

Number of new drug and biologics approvals



Source: FDA

Questions about U.S. adoption

A number of other countries also are considering the use of adaptive licensing strategies to address some of the challenges industry faces. The Singapore Health Sciences Authority, for example, is looking to pilot an adaptive licensing model, and Health Canada has implemented modernization efforts that include key aspects of adaptive licensing, such as benefit-risk science.

In 2012, the President's Council of Advisors on Science and Technology recommended the FDA run pilot projects using existing pathways to explore adaptive approval mechanisms that could collect evidence across the life cycle of a drug. The approach was the subject of an FDA public hearing a year later. Quintiles, the world's largest CRO, also has been at the forefront in calling for the FDA to adopt, on a pilot basis, an alternative development pathway similar to the EMA's adaptive licensing program.

"Data required to determine the efficacy and safety and the benefit-risk profile of a drug can come from a variety of areas. There is value in data that not only comes out of clinical studies, but also is available from electronic medical records, registries and observational studies," said Quintiles' Spaeder. "There are many people in the industry who look at the tools we have available now and are interested in seeing if we can incorporate those tools into the approval process."

Many challenges exist in implementing adaptive licensing as a common pathway for drug approval. Sufficient incentives must be in place to encourage sponsors to continue developing a drug candidate after initial approval. Mechanisms must be introduced to quickly withdraw the medicine if something goes wrong in studies. Other obstacles include biomarker validation and adoption and the need for common data standards. There are questions about intellectual property protection and reimbursement pathways during development. Some of the many other questions include how to limit early access to only the approved subpopulations and who should pay for the ongoing data collection after the initial approval.

Despite those difficulties, many industry leaders believe it's inevitable regulatory models will evolve to include adaptive licensing approaches both in Europe and the U.S. Many researches, including those at MIT's Center for Biomedical Innovation, believe the adaptive licensing model could help address some of the root causes of the overall high cost of drug development. It's broadly acknowledged the cost, size and complexity of clinical trials required to obtain marketing authorization are increasing, and the number of products reaching the market no longer supports R&D activities.

"The current approach simply is unsustainable," said Niese. "It is clear that even with the increasing investments on the development of new medicines, the results are not getting better. In fact, we see a declining number of approvals per billion dollars spent. That can't continue, because at some point in time there will be no money left for development. At the same time, it is critical that the scientific rigor and the assessment of benefit-risk for new medicines is not reduced so the public health is protected. I think the question is how to find the right balance."

Cyril Clark, M.B., B.S. (equivalent to M.D.), vice president of translational medicine at Icon, believes other trends in development, including the move toward personalized medicine and better understanding of the biology of common conditions such as asthma or rheumatoid arthritis—which will target specific treatments to smaller patient populations—also will help lead the industry toward an adaptive licensing model. In addition, while classical trial design for registration has focused on efficacy, he said, payers and patients have become more focused on the drug's effectiveness.

"Effectiveness is how the product actually works in the real world and

the value it provides for the individual patient in the context of costs in an overall healthcare system where judgments have to be made. There is a clear requirement for trial designers to develop data sets that support both efficacy and safety—the traditional regulatory endpoints. But for the last decade, those who have been doing this in an appropriate manner already have been thinking about the end game and reimbursement and effectiveness endpoints and outcomes," said Clark. "The regulatory environment realizes it needs to evolve, but this time it actually is proving to be in step, rather than being fully reactive or one step behind, certainly in Europe."

Industry experts believe necessary pieces, such as tools and data required to identify and monitor patients, already are available in order for the FDA to pilot alternative pathways for drug evaluation and approval. Yet one of the biggest challenges remains getting the public and politicians to understand and accept the idea that drug testing involves a measure of risk.

The current framework for drug licensing relies on the perception that regulators should require sponsors to fully establish safety and efficacy before licensing a drug; to many patients, this implies the drug is 100% safe and effective. Adaptive licensing, however, acknowledges there always will be levels of uncertainty with innovative treatments. Regulators worry this idea might lead to the perception that they are lowering standards, putting the needs of industry before the public and allowing untested drugs on the market. Yet, in reality, no licensing system can guarantee a drug is 100% safe and effective.

"Acceptance from the public at large and the politicians is one of the biggest hurdles to overcome. If regulators approve a product and they have to pull it, which is inevitable, they will be accused of bending over backwards for big pharma," said Beat Widler, Ph.D., managing partner and co-founder of Widler & Schiemann, who worked at Roche for more than 25 years. "We have a risk-adverse society. We enjoy the benefits. But if something goes wrong, we start pointing fingers."

One of the main purposes of adaptive licensing, however, is to gather stronger and more relevant data earlier and throughout the product's life cycle to maximize the benefit-risk profiles of drugs.

In addition, research sponsored by Quintiles found patients are willing to use therapies developed under an accelerated pathway, particularly if they suffer from conditions or diseases with unmet need. A 2012 survey of patients living with chronic disease suggested they want access to new medicines sooner and those in greatest need are willing to accept more uncertainty about taking a new therapy; 72% of patients surveyed in the U.S., and 81% in the U.K. said they should be able to take potentially risky medications, even those not approved for use, if they feel it is their only chance to improve their health.

"Patients who suffer terrible diseases are willing to take therapies and undergo treatments even if there is risk to it, as long as they understand they have a high degree or high likelihood of deriving potential benefit from it," said Quintiles' Spaeder. "We want to maximize the benefit-risk profile. We are aiming to define the patient population that will most benefit or has the greatest benefit-risk profile."

The FDA acknowledges the need for accelerated approvals, especially in therapies with unmet needs, and regulators have written in peer-reviewed journals they believe it likely new regulatory paradigms will evolve during the next few decades. But whether the FDA follows an adaptive licensing path or expands its own accelerated access programs to include elements of this approach will rely on outcome of the EMA's pilot program and other forces, such as whether industry, patient organizations, reimbursers and payers become vocal in their support of the model. While these groups all have different objectives, they share a desire for making decisions based on good evidence.

"The FDA will want to see results of the pilot project. It will want to hear from the regulators in Europe, pharma and biotech companies and patient populations. If there is a demonstrably better and faster way to bring therapies forward, they will be open to incorporating the best of those ideas, just as the EMA will be looking at the breakthrough therapy initiative at the

Drug submissions and approvals

	2001	2004	2007	2010	2013
New NDA submissions	98	128	121	111	132*
NDAs pending decision	110	108	86	106	121
NDA approvals	66	113	68	91	84
NME approvals	24	31	16	15	24

* includes BLAs submitted

Source: FDA

FDA and how that accelerates development," said Spaeder. "I don't think this a matter of one agency is right and one is wrong. They are looking at the same problems and diligently trying to address them. They are focusing on some different approaches. But the data and the evidence will be compelling to all regulators."

Looking ahead

The EMA's pilot program will gather real-world evidence to understand the advantages and drawbacks of adaptive licensing. The experiment's outcome will allow regulators and the industry to understand the technical questions associated with implementation of adaptive licensing and appreciate the perceptions and needs of various stakeholders. With this information, regulators can evaluate whether adaptive licensing ultimately can provide a better alternative to the current licensing paradigm.

While there are many challenges to implementing adaptive licensing as a pathway for drug approval, many see the pilot program as a chance to test an alternative way to evaluate and approve new medicines and move toward a process that allows for better use of data from a variety of sources to assess the risk-benefit profile of a drug.

"The EMA is doing what good scientists do—coming up with a hypothesis and then performing a pilot test to see how this works," said Quintiles' Spaeder. "It may be a wonderful success which they can point to and say, 'Our suppositions were proven correct. And this is something we want to do more.' Or they may come back and say there were unintended consequences or things they never anticipated, some of which may be good, others that may not have been the direction in which they wanted to go."

"It gives them an opportunity to say, 'Maybe we have to recalibrate what we do, expand this, or potentially stop it or wait to see what happens,'" he said. "This is a really interesting way to roll this out in a pilot project."

'Right to Try' laws challenge clinical trial process

20 states pass, 20 more pending allowing access to study drugs without FDA & IRB approval

Should terminally ill patients be able to step around expanded access programs to gain access to investigational drugs simply because they believe, with the support of their doctor, that they will benefit?

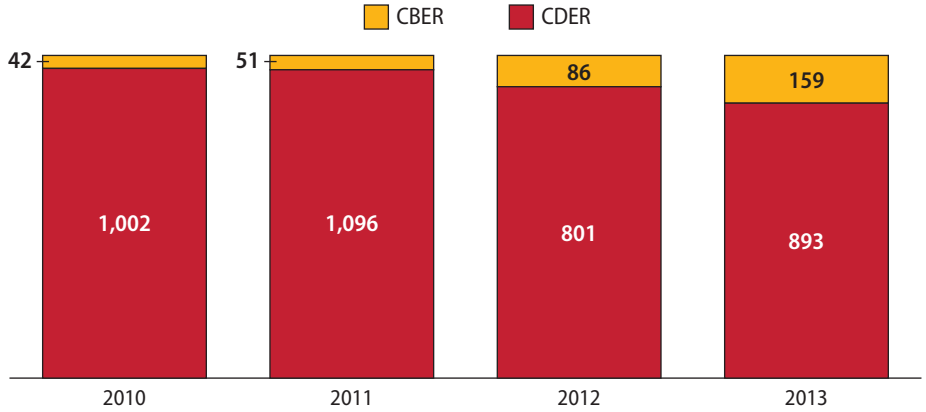
Many state governments believe the answer should be yes.

Since early 2014, Right to Try laws have passed in 20 states, and currently, more are pending in 20 additional states.

The laws grant patients access to investigational drugs if they have a terminal illness, they've considered other options and their doctor will give them a prescription for it. Biopharmaceutical companies can choose to sell the drugs to patients or they can offer the drug for free. None of the new state laws specifies that the drug sponsors must offer the investigational treatment free of charge.

The laws purport to make the process faster and easier on patients than the FDA expanded access program. The Expanded Access to Investigational Drugs for Treatment Use program opens the gates for terminally ill patients to get experimental drugs if their doctor deems that they have no other treatment alternatives, if access to the drug will not interfere with clinical trial activity, the data thus far shows the drug to be safe and the drug sponsor is willing to give the patient the drug. These programs, often referred to as "compassionate use," require FDA approval as well as review and approval by an Institutional Review Board (IRB). About 1,000 people applied to receive experimental agents through this program from 2009 to 2013, and virtually all were told yes.

Expanded access INDs submitted by year



Source: FDA

But critics of the FDA's expanded access program say it's too slow, that the paperwork is burdensome and the approvals process takes too long. Right to Try laws, they argue, will speed matters up for the dying who feel that their only hope lies in drugs that haven't yet reached the market.

Others say the Right to Try movement is mostly a libertarian initiative started by the Goldwater Institute, a conservative organization whose leaders don't like the regulatory power wielded by the FDA.

"The sickest Americans don't have the luxury of time to wait for these drugs to come to market through the traditional process," said Christina Corieri, healthcare policy analyst at the Goldwater Institute, in published reports. "The Right to Try Act puts the decision about whether to try an experimental treatment back where it belongs: in the hands of patients and their doctors."

Currently, after an investigational drug has successfully completed phase I testing, it can take an additional six or more years for that drug to be approved for market even if clinical trials are demonstrating safety and efficacy. That's not fast enough, say critics.

The Goldwater Institute came up with a draft for Right to Try legislation, and several states have used it. The state of Arizona used it almost verbatim in getting its laws passed.

The Pharmaceutical Research and Manufacturers of America (PhRMA)—though it has not released an official statement on the movement—is not pleased about it, and would rather see patients gain access to investigational drugs under the oversight of the FDA and IRBs.

"We have serious concerns with any approach to make investigational medi-

cines available that seeks to bypass the oversight of the Food and Drug Administration and clinical trial process, which is not in the best interest of patients and public health," said Sascha Haverfield, PhRMA's vice president of scientific and regulatory affairs, in a statement.

"The clinical trial process is the primary mechanism by which patients may participate in the drug development process and receive access to unapproved investigational medicines," he continued.

Those in research fear the movement—providing access to single patients when they ask—may result in slowdowns of the clinical trial process that brings drugs to market for thousands or more people. After all, if people can just request the drug, why participate in a clinical trial in which you might end up with placebo?

"Such programs pose real risks: conduct of an [expanded access program] may jeopardize enrollment or retention of patients in ongoing clinical trials of a drug that determine safety and efficacy and ultimately gain regulatory approval," wrote Merck executives Michael Rosenblatt and Bruce Kuhlick in a viewpoint piece that appeared in the *Journal of the American Medical Association* in May.

And if the patient using an experimental drug has a bad reaction, that can complicate a drug's safety profile, even when the cause of the reaction isn't clear, and this could further slow approval, they pointed out.

"Thus," Rosenblatt and Kuhlick wrote, "in responding to patient's understandable requests for compassionate access before approval, companies need to consider not only their concerns but also society's greater interest in development and availability of the drug for the larger group in need."

Others in the industry are concerned that the program could become expensive for them, siphoning off the often very expensive compounds manufactured for trials, while removing the opportunity for the drug maker to collect data.

20 States that have passed Right to Try laws

- Alabama
- Arizona
- Arkansas
- Colorado
- Indiana
- Louisiana
- Maine
- Michigan
- Minnesota
- Mississippi
- Missouri
- Montana
- Nevada
- North Dakota
- Oklahoma
- South Dakota
- Tennessee
- Utah
- Virginia
- Wyoming

20 States with pending Right to Try laws

- Alaska
- California
- Connecticut
- Delaware
- Florida
- Georgia
- Hawaii
- Illinois
- Kansas
- Massachusetts
- New Hampshire
- New Jersey
- New York
- North Carolina
- Oregon
- Pennsylvania
- Rhode Island
- Texas
- West Virginia
- Wisconsin

Confluence of factors

The Right to Try movement got kicked up last year after the 2013 Academy Award-nominated movie "Dallas Buyers Club" drew attention to the story of Ron Woodruff, a Texas man stricken with AIDS in the 1980s who smuggled unapproved drugs into the U.S. and sold them to the growing number of AIDS patients who had virtually no treatment options, as the disease was so new.

But it's not just the movie and the Goldwater group. Also urging the Right to Try movement forward is a confluence of other factors, said Ross Upshur, director of the University of Toronto Joint Center for Bioethics, and a member of the World Health Organization's committee looking at compassionate use for vaccines.

"The pipeline is choked with bureaucracy, then add Google and the internet, and suddenly not only is everyone a doctor, but everyone is also a researcher and a scientist," he said. "This has changed the landscape dramatically. The person with the disease, or their family, will comb the internet and can come to know more about the disease than their doctor ever will, and that's where you run into Right to Try."

The case of Joshua Hardy received a lot of attention last year. Joshua is a now 8-year-old-boy who contracted a life-threatening adenovirus infection following a bone marrow transplant to treat his cancer. The standard-of-care drug being used to treat his infection was harming his kidneys, so he had to be taken off the drug. His family learned of the biotech company Chimerix's compound Brincidofovir, an anti-viral agent designed to avoid harm to the kidneys. The drug was in phase III trials focused on a different type of infection.

The family asked Chimerix to provide access to the investigational drug for Joshua. The company initially said no, fearing that the drug's clinical trials would be undermined. The Hardy family went public with the company's refusal, and it became a storm on social media as well as in traditional press outlets, ultimately resulting in death threats to Chimerix's CEO. The company responded by creating a new clinical trial that focused on Joshua's illness. He participated, and ultimately recovered.

Upshur thinks the Right to Try movement will pick up even more steam as more breakthroughs occur in precision medicines that are targeted to receptors rather than diseases.

This year, Johnson & Johnson reached out to bioethicist Art Caplan to find a good way of dealing with Right to Try, since Caplan—founding director of the Division of Medical Ethics in NYU Langone Medical Center's Department of Population Health—leads the only independent group tracking Right to Try and compassionate-use issues.

The problem for drug makers? The patients who know how to wage a social media campaign and press the hardest—like the Hardys—are most likely to get access to the drugs, while the quieter ones are not, said Caplan. J&J wanted to even that out, so Caplan helped set up a committee and a system for handling requests anonymously.

"There's no lobbying the members or calling the chair," he said. "This makes it fairer for everyone."

Caplan says he foresees more sponsor companies setting up such committees, as the number of Right to Try requests picks up. Others note that sponsors could benefit by gathering additional data about investigational drugs under Right to Try programs if they had the infrastructure to do so.

Potential harms

Research sponsors are thinking things through.

Caplan predicts that companies will begin manufacturing larger quantities of investigational treatments and put some aside for Right to Try requests.

Several sponsors are considering charging patients to help defray the increased manufacturing and distribution costs.

But what of the harm that investigational drugs can cause? That's what worries Upshur. "There's a big misconception here: that we have miraculous cures in trials, when only something like one in 100 of the compounds in trials will make it through phase III, and these compounds have equal capacity to do harm as to do good," Upshur said. "There's a very good reason the regulations are in place: to protect people from possible harm while we make that assessment."

There's a lot of press as each new state passes a Right to Try law, but Caplan says he doesn't think it will result in any great shift in the way the industry conducts itself. After all, federal regulations already exist via the FDA that does much the same thing.

"The new laws don't create an obligation for companies to give anything to patients, rather, it offers patients a right to beg, which they had anyway through the FDA's expanded program," said Caplan.

And the FDA recently made some changes to its expanded access program to make it quicker and more responsive, with less paperwork, and with doctors making the decision, not the FDA, said Caplan. The vast majority of requests for investigational drugs for terminal patients are granted, so the agency is not a roadblock, as the Goldwater Institute might have the public think, he said.

"As far as I've been able to tell, the Right to Try movement is just a public relations campaign criticizing the FDA, perhaps with the goal of trying to get the government to do something to speed up the drug approval process overall," Caplan said. "But it does send a message from the grassroots level that people are interested in doing something about this."

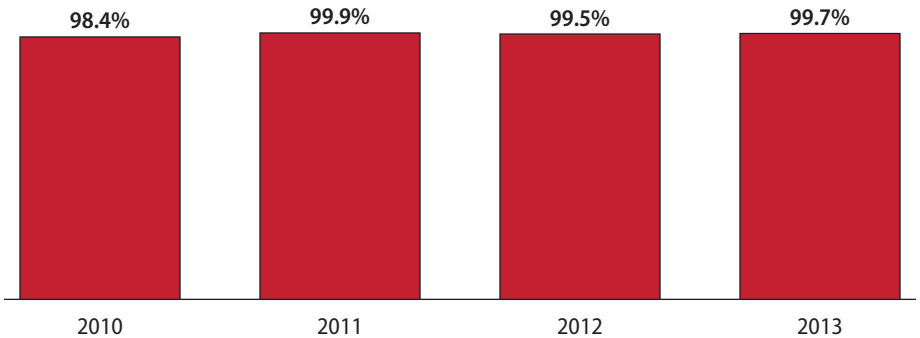
With this ironic twist, he added, "The people pushing these laws are the same people who are pro-business, so these laws don't obligate drug companies to

Contrasting expanded access and Right to Try programs

Expanded access	Right to Try
Requires FDA approval	Patient has a terminal illness
Requires institutional review board approval	Patient has considered other options
Doctor declares that patient has no other alternatives	Patient's doctor will give them a prescription for it
The patient's access to the drug will not interfere with a clinical trial	Investigational drug has successfully completed phase I
Data so far on the drug shows it to be safe	Sponsor company can choose to offer, and to charge for, investigational drug
Sponsor company can choose to give, and to charge for, the investigational drug	

Source: CenterWatch

Proportion of expanded access IND requests approved



Source: FDA CDER

give patients their compound for free, nor do they offer help with travel or getting to the drug," Caplan said. "They won't go there."

At the end of the day, the drug approval and commercialization process is regulated by the FDA. "However well intentioned," said PhRMA's Haverfield, "legislation at the state level isn't likely to add any meaningful new approaches that can optimize the federal government's expanded access process overseen by FDA."

Will Right to Try laws result in terminally ill patients getting fast access to experimental drugs? The jury is still out. No one has yet taken advantage of a Right to Try law.

Stay tuned.

A Statement from PhRMA on the Right to Try Laws?

The Pharmaceutical Research and Manufacturers of America (PhRMA) does not have an official position on Right to Try laws, but when CenterWatch inquired, the organization sent this statement from Sascha Haverfield, vice president of scientific and regulatory affairs:

We have serious concerns with any approach to make investigational medicines available that seeks to bypass the oversight of the Food and Drug Administration (FDA) and clinical trial process, which is not in the best interest of patients and public health.

The clinical trial process is the primary mechanism by which patients may participate in the drug development process and receive access to unapproved investigational medicines. Successful completion of the clinical trial process is necessary to demonstrate that an investigational medicine is safe and effective, which is required to obtain FDA approval, so that companies may make the medicine available to a broader patient population when clinically appropriate.

For patients with a serious or life-threatening disease who are ineligible or unable to participate in a clinical trial, use of an unapproved investigational drug via an expanded access program may be an option.

The FDA process for a patient to gain access to an investigational drug through expanded access was established in 2009 in close consultation with patients, physicians and the biopharmaceutical industry. Legislation at the state level, however well intentioned, is unlikely to add any meaningful new approaches that can optimize the federal expanded access process overseen by FDA.

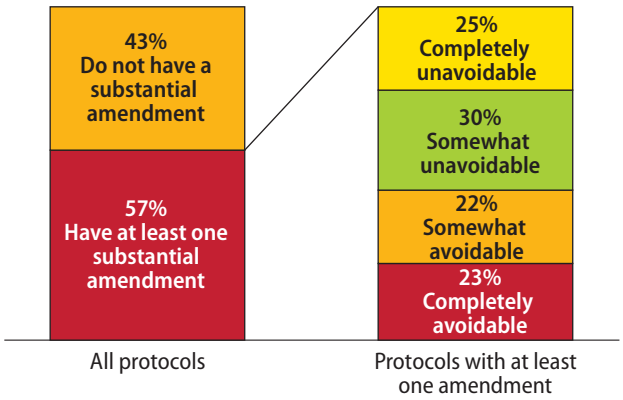
Instead, all stakeholders—patients, physicians, biopharmaceutical companies, academia and FDA—must come together to identify ways to improve the existing federal expanded access process and modernize the clinical trial, drug development and FDA review processes by harnessing 21st century science to accelerate the availability of new medicines for the patients who need them.

Facing protocol amendments head-on

Cycle time and cost impact shining light on avoidable amendments

The unplanned costs and delays associated with protocol amendments have prompted many sponsor companies to identify new approaches to simplify protocol designs and reduce the frequency of protocol amendments over the course of the past few years. Yet a new Tufts Center for the Study of Drug Development (CSDD) analysis found that the majority of protocols still require substantial amendments, which led to significantly longer clinical trial cycle times and higher costs.

Prevalence and avoidability of amendments



Source: Tufts CSDD, 2016 <csdd.tufts.edu>

The new analysis builds on a 2010 Tufts CSDD study that, for the first time, quantified the prevalence and causes of protocol amendments. It found that 57% of protocols had at least one substantial amendment and nearly half (45%) of these amendments could have been avoided, compared to 33% in 2010. About one in four (23%) amendments were implemented before the first patient was dosed.

On average, clinical trials with at least one substantial protocol amendment took three months longer to complete than those without an amendment. Overall, the Tufts CSDD estimates protocol amendments cost the industry a total of $20 billion a year in direct and indirect costs.

"It's a call to action," said Rob DiCicco, Pharm.D., vice president of Clinical Innovation and Digital Platforms at GlaxoSmithKline (GSK). "It may be that different initiatives that companies started a few years ago aren't reflected in the data or that the problem is getting worse because of a variety of factors, including protocol complexity. Either way, there is a massive opportunity for improvement."

The peer-reviewed study findings, published in the journal *Therapeutic Innovation & Regulatory Science*, link protocol amendments to performance measures for the first time and offer opportunities for companies to better understand the impact of major changes to finalized protocols.

In the following, CenterWatch looks at highlights from the new Tufts CSDD study and initiatives at forward-looking companies—including Amgen, Pfizer, GSK, Eli Lilly and Parexel—that are designed to improve the quality of study design, reduce the frequency of protocol amendments and better inform the decision-making processes.

Amendments impact performance and cost

The 2015 Tufts CSDD study, which was based on data from 836 protocols provided by 15 large and mid-sized pharmaceutical and biotechnology companies and CROs, found small signs of improvement in reducing protocol amendments compared to the 2010 study, but the frequency of substantial amendments remained high. The study defined "substantial amendment" as any change to a protocol on a global level requiring approval both internally and from a review board or regulatory authority.

The incidence of amendments in the 2015 study (57%) was below that observed in the Tufts CSDD 2010

study (69%), which might reflect early results from new industry practices designed to reduce protocol amendments. The study authors believe the difference largely could be explained by changes in the 2015 study methodology. The previous survey counted country-specific amendments and those from ongoing studies, while in 2015, only completed protocols and global amendments were included.

Two-thirds of phase III protocols were amended, with an average of 2.3 amendments per protocol. The median direct cost to implement a substantial amendment for phase III protocols, which are typically larger and costlier than earlier phases studies, was $535,000, a higher amount than originally expected. The Tufts CSDD report estimated that total indirect costs for a phase III protocol amendment could be three-to-four times larger. Meanwhile, phase II trials had the highest proportion of substantial amendments (77%), averaging 2.2 amendments per protocol, with a median cost of $141,000 to implement.

GSK's DiCicco said the study results suggest sponsor companies should focus efforts to reduce protocol amendments on phase III, where the programs are more expensive, take longer to deliver and the risk around making protocol changes carry an element of regulatory risk. "You know more when you go into phase III and ought to be in a better position to get it right," he said.

While the frequency of protocol amendments decreased between 2010 and 2015, the Tufts CSDD observed that the number of changes per amendment has increased, suggesting that sponsor companies are using new strategies to reduce the number and expense of protocol amendments. Instead of making numerous amendments, some companies have begun to hold off on non-urgent changes and bundle them into the next major amendment that arises. Since the largest costs associated with amendments are for institutional review board (IRB) fees and change orders to vendor contracts, the approach can result in cost savings for companies.

Phase II and phase III amendments

	Phase II protocols	Phase III protocols
Percentage of protocols that have at least one substantial amendment	77%	66%
Mean number of substantial amendments	2.2	2.3
Median direct cost to implement each substantial amendment	$141,000	$535,000

Source: Tufts CSDD, 2016 <csdd.tufts.edu>

"We have learned that we should be waiting for a significant amount of changes to be required prior to implementing an amendment. So hopefully we are doing something right," said Derek Dunn, associate director of Global Clinical Operations at Alexion Pharmaceuticals. "Each time you submit an amendment to a regulator and an ethics committee, you get charged for review. There are many internal and external costs, so if you could wait and batch things together and just do an amendment once, it just makes more sense."

Sponsor companies have also become better at evaluating their own protocols and determining whether amendments could have been avoided. While the proportion of avoidable amendments increased by 12 percentage points since 2010, the Tufts CSDD study noted that the finding might be due more to the study's classification system than an observed trend. Study participants had a better understanding of how to classify amendments in the 2015 study and were less conservative in what they considered an "avoidable" amendment.

"Clinical trial sponsors are spending an increasing amount of time and effort to ensure that they are correctly classifying the cause of amendments," said Mike Capone, chief operating officer at Medidata Solutions. "For example, the increased availability and visibility into historic enrollment performance shows us very clearly that certain amendments related to participant enrollment and retention—such as eligibility criteria and demographics—are avoidable."

Nevertheless, nearly half of all substantial amendments could have been prevented. While amendments are implemented for a variety of reasons, including the availability of new safety data and regulatory agency requests, the top reason for amending a protocol is to change study volunteer eligibility criteria because of changes in study design strategy and difficulties in recruiting patients. More than half (62%) of substantial amendments were implemented during the study enrollment period.

"A high proportion of these amendments are viewed by companies to be avoidable. It really calls us to action. If we can prevent these avoidable amendments, then we can really effect the cost of drug development and the speed with which we get life-changing medicines to patients," said Jules Desmond, Ph.D., development design director of Am-

gen's newly instituted Development Design Center.

The Tufts CSDD report also found that protocols with even one amendment had a substantially lower number of patients screened and enrolled compared to the original plan. Although the amendments had the desired effect of lowering the number of patients needed to complete the study, which can lower study costs, Tufts CSDD said those savings must be offset by the longer cycle times and direct costs of implementing an amendment. In addition, reducing the number of patients in a study could weaken the statistical quality of the data and which signals will be detected.

"If they can't do their power calculations or even their descriptive statistics based on a smaller number of patients, it's not going to fly," said Alexion's Dunn.

Amendment occurrence by phase

Phase	Before first patient dose	During enrollment	During study maintenance
Phase I	40%	50%	10%
Phase II	18%	70%	12%
Phase III	15%	65%	20%
Phase IIIb/IV	33%	67%	0%

Source: Tufts CSDD, 2016 <csdd.tufts.edu>

Redesigning the study development processes

Partly in response to the 2010 Tufts study, a growing number of research sponsors have begun to keep metrics on the frequency of protocol amendments, evaluate their protocol design practices and implement new governance mechanisms and processes to improve protocol designs and reduce complexity. In addition, half of the companies that participated in the Tufts CSDD research have begun setting aside funds to assess the cost of amendments and manage unplanned increases in study budgets.

"Drug companies are very cognizant of the impact of amendments to trials and their businesses. Sponsors are increasingly leveraging new technologies in protocol design optimization, investigative site and patient feedback panels and protocol review committees to help mitigate the impact of protocol changes," said Medidata's Capone.

Amgen dramatically changed the way it designs programs and individual studies by initiating a new design process last year that incorporates cross-functional, data-driven and real-time development principles. A new clinical development capability, called the Development Design Center, partners with teams to design better program-based studies. The center brings data sources; predictive analytics; local expertise resources, including feasibility managers in countries worldwide; and specialist clinical development expertise. The center packages these elements into a framework for teams that helps facilitate decision-making and better understanding of the impacts of various design trade-off decisions. Once data has been collected and options mapped out for teams, the process ensures all decision-makers have the chance to discuss the information in a collaborative manner.

"We believe the greatest opportunity to affect cost and cycle times exists at the time you design programs for studies. This Tufts study reaffirms it," said Desmond. "The ability to reduce substantial amendments is or will be a key contributing factor to savings. But rather than address the proximate cause of amendments on a case by case basis, we like to frame amendment reduction as being a by-product of good design. So we asked ourselves, how can we improve our design process at Amgen?"

As part of the changes, study design was separated from protocol authoring in order to realize time savings and focus individuals on study design in the initial stages. During the design portion, teams develop all of the design elements for the study along with an operational plan to ensure the design can be executed. The study design then gets reviewed and approved in a first stage of governance. The study design moves to a protocol-authoring step, where the design is translated into a protocol. At this point, the design is locked-down and cannot be challenged. While the protocol is being produced, the rest of the organization can begin study startup activities based on the approved study design.

"That is where we save time. We are not waiting around for a final polished protocol before we begin study start-up work internally," Desmond said. "Once the protocol is complete, it is reviewed/approved in a second stage of governance."

At Lilly, a series of protocol improvement initiatives was adopted in 2013 to strengthen protocol quality and feasibility up-front in order

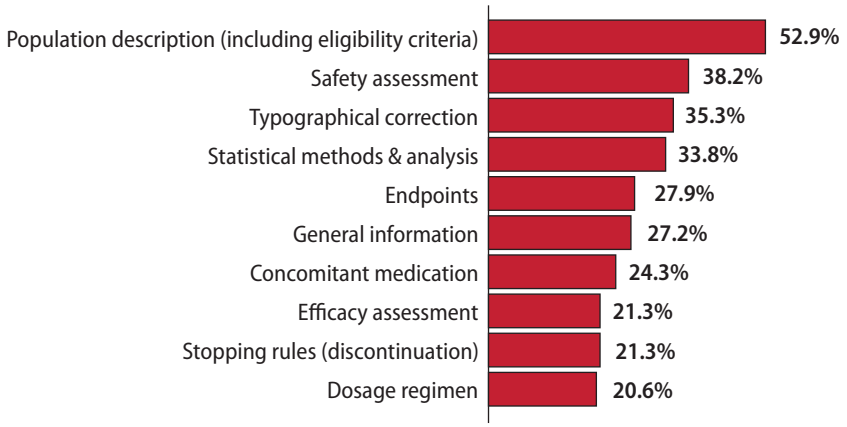
to reduce the types of amendments caused by planning issues, such as recruitment or investigator requests, or those associated with errors or inconsistencies within the protocol. The initiatives were aimed at three specific objectives: simplify and focus the protocol design, incorporate patient-centered approaches and streamline the drug development process.

The initiatives included a redesign of the study development process for phase II-IV programs to better engage patients, study sites and investigators. One effort uses feedback from patients about their clinical trial experiences to inform future protocol design. Once the initial concept of the study has been determined, patients and study coordinators simulate the protocol while the study team watches in order to identify and address feasibility issues that could potentially trigger amendments before protocol approval.

Study teams learn about the new process through training workshops held just before the design phase begins for a clinical trial, which allows them to talk about feasibility issues within the context of a specific protocol and receive support in implementing changes identified through the program. The clinical research physicians and scientists who write protocols also participate in training sessions focused on improving the clarity and effectiveness of protocols along with minimizing non-essential protocol requirements.

"We want our study teams to recognize that the greatest cost of needing to amend a protocol for feasibility or planning issues is the extension of the clinical study duration," said Mary Short, research advisor at Eli Lilly. "We have been committed to finding innovative ways to improve the speed and quality of our development processes so that we can actually get new medicines to the people who need them faster."

Top areas addressed by amendments



Source: Tufts CSDD, 2016 <csdd.tufts.edu>

Lilly measures the impact of its protocol improvement initiatives using a specific time frame: from protocol approval to within 100 days after the first patient visit. Since the program began in 2013, Lilly has seen a 50% reduction in amendments that were related to feasibility, recruitment, investigator requests and planning. The new processes also resulted in a significant reduction in the number of amendments due to internal errors, inconsistency or a need for clarification.

Protocol review processes

Both Pfizer and GSK have implemented extensive internal review processes to improve protocol quality and reduce unplanned and unbudgeted amendments.

At Pfizer, protocol review committees have been used for many years by some groups across the organization, depending on therapeutic area or phase of development. The company recently revised its organizational standard operating procedure (SOP) to require that all protocols go through a detailed protocol and amendment review prior to implementation. The protocol development has been distilled into a three-step process that will be applied universally to all protocols across the organization.

The first step of the process calls for a review by a senior management governance committee in the applicable therapeutic area. This review is intended to achieve consensus on the design elements of the study and ensure the protocol is consistent with the overall development plan for the asset. This review committee endorses design elements such as inclusion/exclusion criteria, objectives and endpoints and dose selection. The study team then writes a detailed protocol, which goes to an independent review committee made up of a diverse group of individuals, including clinicians, statisticians, clinical pharmacologists and operations experts. The group reviews the entire document to ensure consistency, readability, operational feasibility, clinical safety and scientific integrity.

The last step is a technical quality control review where a group of individuals familiar with the various protocol templates used at Pfizer further ensure consistency across sections of the document. This group also makes sure that study teams have used the

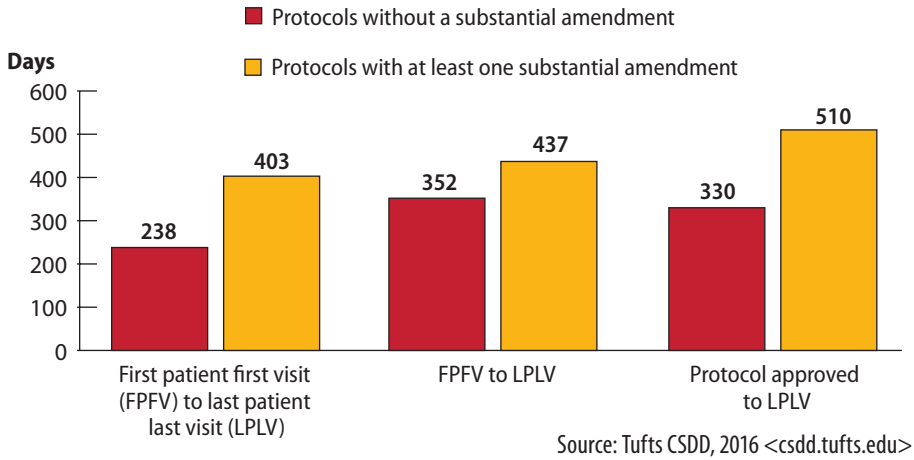
correct template for their protocol and that all mandatory information has been included.

"The overall goal is to improve protocol quality, better ensure study success, reduce the number of protocol deviations and reduce the number of protocol amendments," said Pfizer Executive Director David Kazierad, Pharm.D., who is the clinical lead in the cardiovascular metabolic research unit and business process owner (BPO) for protocol authoring.

GSK, which began one of the earliest facilitated clinical review processes in 2011, has reduced the average number of amendments per protocol by more than 20%. All phase II and III protocols are reviewed by a panel of experts, both from clinical and operational roles, late in the development stage. GSK considers the process a good return-on-investment because study teams don't need to create new materials for the review; they are asked to give the committee whatever information they already have. The peer-review group uses regulatory correspondence, and the protocol and what they know about the space, to ask whether the inclusion/exclusion criteria are realistic, if all of the procedures are necessary and linked to important endpoints in the protocol, whether the burden on patients is reasonable and if the protocol aligns with feedback from regulators. The review team makes recommendations about the protocol, but the final decisions about changes are made by the study and project teams.

"If you marry the Tufts report to their prior work on protocol complexity, which looks at the amount of data collected, the number of procedures that are performed and whether or not they are actually related to a primary endpoint, the two things go hand-in-hand. For the teams that go through our facilitated review process, there is a clear reduction in amendments. The issue then becomes a question of whether 20% is enough? The answer is probably not," said GSK's DiCicco.

Impact of implementing an amendment on study cycle times



Source: Tufts CSDD, 2016 <csdd.tufts.edu>

Other industry initiatives underway

Last year, Parexel launched its Clinical Development Optimization process and service offering, which includes a component aimed at reducing flaws in protocol design that can lead to amendments and study delays. Standard protocol elements—including endpoints, sample size, study design, study procedures and inclusion/exclusion criteria—are evaluated to determine whether the protocol makes sense from scientific, regulatory, operational and commercial perspectives. Protocol feasibility can be tested in silico, using modeling and simulation in virtual populations, and in practice through Parexel's phase I units. As part of the evaluation, Parexel generates alternative designs or approaches to running the same study.

"If we spend more time up front, it will pay off handsomely later. In particular, we should spend more time compiling and reviewing our study protocols and conducting proper feasibility regarding the intended study population and the standard-of-care around the world. Doing this well, even if it takes a little bit longer, will almost inevitably end up saving time and money in the longer term," said Sy Pretorius, M.D., chief scientific officer at Parexel.

TransCelerate BioPharma, a nonprofit organization comprised of about 20 of the largest pharmaceutical and biotechnology companies, has made protocol feasibility one of its top areas of focus, and recently released a common protocol template that can promote greater efficiency in protocol review processes. More than 90 entities, including member companies, government agencies, academic institutions and small biotech companies already have downloaded the template from TransCelerate's website.

DiCicco, the workstream leader for TransCelerate's Common Protocol Template project, said that by using a common structure and model language for protocols, it becomes more obvious when there is a misalignment between protocol objectives and endpoints in data collection. The common protocol template also makes automation possible. This allows companies to reuse libraries of information instead of

recreating them manually, which could lead to human error.

Automating a common protocol template also sets the stage for using advanced analytics to inform protocol design and improve protocol performance.

DiCicco said clinical areas have been slow to adopt the type of quality by design processes used by the manufacturing, laboratory and preclinical areas. Yet he said various industry initiatives, including feasibility review committees, common protocol templates, investigative site and patient feedback panels, all have the potential to "review quality back into the protocol."

DiCicco said, "There isn't one magic potion or one magic solution. It has to be the quality by design element, harmonization and simplification of protocols through things like TransCelerate, and it has to be modernization of the clinical trials process where you can actually use analytics from the data that you have to inform your protocol."

Looking forward

As sponsor companies face growing pressure to accelerate the development of new drugs while reducing costs, the Tufts CSDD study findings provide opportunities to better manage and reduce significant costs and delays associated with major changes to finalized protocol designs. Sponsor companies and CROs should continue to develop programs and mechanisms that challenge the executional feasibility of their study designs and help prevent avoidable amendments.

"The prevalence of substantial amendments remains high," said Desmond. "It's very powerful for an organization to actually see on paper what the effects are in terms of cycle-time increase and financial cost increase. We owe it to our patients to get our medicines to them quickly and minimize delays wherever we can. Studies like this really focus our attention on areas that we can improve."

Mixed experience with the Sunshine Act

Open Payments process smoother but adding burden for sites

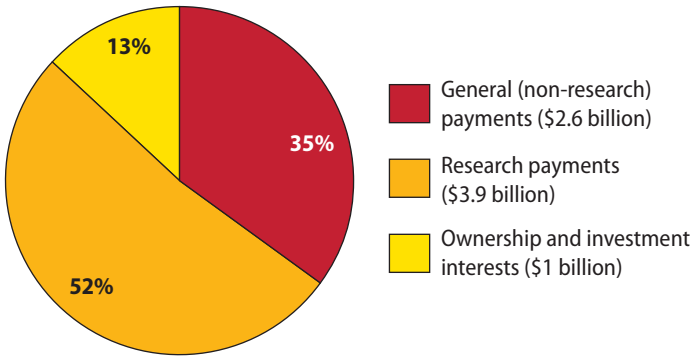
Pharmaceutical companies have finished submitting the third batch of data detailing their financial relationships with physicians and teaching hospitals under the Open Payments program, also referred to as the Physician Payment Sunshine Act. Investigators now face the prospect of implementing sophisticated new processes and systems that can track and verify clinical research grant payment information.

The increasing burden associated with Open Payments regulatory requirements already has resulted in some investigators, particularly private practice physicians who conduct clinical research part-time, leaving the clinical research enterprise or cutting back on their participation.

"Research has become much harder than it was 10 or 15 years ago. It's gotten more complex. We are struggling just to stay above water. It's hard, when you are struggling, to add more layers," said Ana T. Marquez, founder and CEO of Marquez Clinical Site Partners and a site owner and chief financial officer for a number of research sites in Florida.

For pharmaceutical companies, the recent reporting cycle has been fairly straightforward and lacking in controversy, compared to previous years, and many of the initial problems related to data submission have been resolved. Companies applied lessons learned from prior reporting periods to their processes, and communications have improved between sponsors and the Centers for Medicare & Medicaid Services (CMS), which manages the program, concerning reporting and technical requirements. Both sponsor companies and investigative sites also have become more familiar with the CMS Open Payments reporting template.

Distribution of 2015 Sunshine Act payments to physicians
(Total: $7.5 billion)



Source: Centers for Medicare & Medicaid Services Open Payment Report

"Companies experienced far fewer challenges submitting their data to the system than they had in prior years," said Lauren Roth, assistant general counsel for the Pharmaceutical Research and Manufacturers of America (PhRMA), a trade group that represents research-based pharmaceutical companies in the U.S. "Interacting with the Open Payments system has, in general, improved."

Yet the impact of Open Payments on investigative site operations is less understood, and the full effect of its implementation will not be clear for several years. Sponsors and CROs have added contractual requirements for sites to track and report third-party payments, which have the potential to add cost and time burdens, yet many investigative sites don't fully understand the obligations or fail to comply. Some sponsors have begun asking investigators to validate payment information prior to publication. An overly complex registration process and inadequate review period, however, has prevented many investigators from participating in the CMS data validation process and has raised questions about the accuracy of the information posted.

Investigators have criticized the method used to report research payments, arguing that it misrepresents the amount of money principal investigators (PIs) receive in support of clinical trials, and expressed concerns about the implications of reporting

monies paid through a research grant in the same database as lunches provided by industry to physicians. In addition, many clinical research professionals fear that publicly reporting industry payments to individual physicians could wrongly imply that the payments are inappropriate and result in a chilling effect on the enterprise.

Number of Sunshine Act payments to physicians reported

	2014	2015
General payments	11.2 million	11.1 million
Research payments	672,969	764,679
Ownership and investment interests	5,268	4,322

Source: Centers for Medicare & Medicaid Services Open Payment Report

Third-party reporting requirements

The Open Payments program, a provision of the Affordable Care Act, requires pharmaceutical and medical device companies to report payments to physicians and teaching hospitals, including clinical research grants, for publication on a searchable public database. The submission process has become more routine since the database was launched in 2014, yet the large amount of information that must be reported and the complexity of collection processes has required massive investments in systems and manpower; as of June, a total of 28.2 million records have been published on the Open Payments website. PhRMA members, who spent tens of millions of dollars establishing new processes and systems to comply with the law, have reported that annual ongoing costs can range from $2 million annually for a mid-sized pharmaceutical company to more than $5 million each year for large companies, amounts that far exceed the original CMS estimates.

Penalties for noncompliance and inaccurate or late reports range from $1,000 to $100,000 per transaction, with a maximum annual penalty of $1,150,000 per company. In its 2016 report to Congress, the CMS said it has used targeted education and outreach efforts to increase compliance during the first few years of the program, yet the agency has indicated it will begin enforcing the Open Payments program by auditing data submissions and imposing civil monetary penalties where appropriate.

Many sponsors have implemented process changes that include contractually requiring CROs and other service providers to document and submit payments made to investigators on their behalf, which adds to the overall financial burden created by the Open Payments requirements. Vendor contracts also increasingly include potential penalties for third parties who fail to report these payments in an accurate or timely way.

"We have had to implement a number of additional processes to ensure that we can provide our sponsor clients with all the information they feel is required for them to properly comply with the Open Payments reporting. Some of these costs we have absorbed ourselves, and others we have passed onto our sponsor clients. There is no doubt that this requirement has added cost to the overall clinical trial process," said Stuart Thiede, president of payments at DrugDev.

Similarly, although physicians themselves are not required to file reports under Open Payments rules, research contracts increasingly include language that references Open Payments processes and requires investigators to track and report research payments made to other physicians involved in the study. If research funds were used to compensate another doctor for reading an X-ray, for example, or if part of the study was outsourced, the investigator would need to report those payments back to the sponsor. Site management organizations (SMOs) that receive clinical research payments and distribute them to investigators in their network would face similar reporting requirements.

Some investigators have taken steps to avoid the additional administrative burdens imposed by the third-party reporting requirements. Michael J. Koren, M.D., CEO of the Florida-based Jacksonville Center for Clinical Research and one of its PIs, said contracts are written in a way that allows sponsors to fulfill their own reporting requirements without requiring investigators to submit additional data. Christine Pierre, founder and president of the Society for Clinical Research Sites (SCRS), said other investigators negotiate to have the CRO or sponsor company contract directly with third-party investigators or vendors needed for the study rather than involving the investigative site in those transactions.

"That puts the burden back on the sponsor or CRO," said Pierre. "Studies are obviously very complex today and many times it requires investigators to go outside of the actual clinical research site to successfully execute

them. We need third-party vendors. When those situations occur, it requires recording methods that have to be sent to the sponsor. It's an added burden."

To date, however, the vast majority of investigators contacted by CenterWatch for this story report that while research contracts include language about additional data tracking and reporting responsibilities required as a result of Open Payments, the cost and administrative implications so far have been minimal.

"The overall impact of the Sunshine Act has been essentially nil as of now," said Mark Lacy, president and CEO of Benchmark Research, a clinical research firm with six U.S. locations. "Whether that changes, who knows. But for now, the [impact] has been an industry exaggeration, from my view."

Marquez said that when she speaks to investigators about Open Payments requirements, most are unaware of contractual third-party reporting requirements and have not set up internal processes to review payment information. Since many investigators don't handle administrative matters and instead have finance directors or other staff members manage contracts and other paperwork, she said, they often don't fully understand the Open Payments program or its impact on site operations.

"Many investigators still don't know about the law and are surprised to learn that the research payment information is posted on a public website," she said. "I don't think sites truly understand their obligations. There is also a lot of ambiguity."

Verifying accuracy of data

For PIs, processes required to monitor the grant payment information attributed to them on the CMS website and correcting inaccurate reports are time-consuming and complicated. Investigators are advised to routinely maintain records of research payments received and amounts paid to third-party vendors in order to verify and challenge information, if needed. Some sponsor companies also ask investigators to verify payment information before it's published. But many investigators, particularly physicians who conduct research part-time, lack the mechanisms for good payment tracking and reporting systems.

"Sites really don't have the infrastructure to double-check figures, so that is not happening at the site level," said Marquez. "We are already bogged down in paperwork and have trouble keeping up because, unfortunately, we are having to take on more work in other areas. The last thing we have time for is verifying what is going to be reported."

Once sponsor companies submit payment data to the CMS, physicians and teaching hospitals have 45 days to review the payments attributed to them and 15 days after that to dispute and correct the data. If the dispute has not been resolved within 15 days, CMS will publish the data with a note that the payment is under dispute. The American Medical Association, in a statement issued in June when the CMS released 2015 Open Payments data, said the resolution process was too short and complex for physicians to review and correct any inaccurate data within the 60-day timeframe.

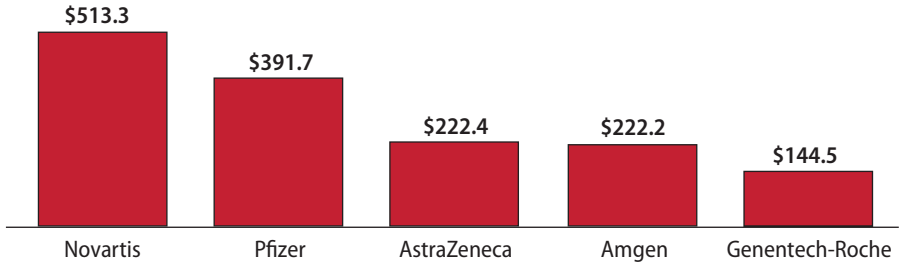
"The sites have a very tight window to review and dispute all of the payment information reported by sponsors," said DrugDev's Thiede. "This can be a very difficult and labor-intensive exercise for the clinical trial site because their internal systems typically are not robust enough to efficiently carry out such an exercise."

Although the Open Payments process has been in place for more than two years, registration challenges and continued data errors have prevented many physicians from participating in the review and validation process. The AMA has called the registration process "time consuming, non-user friendly and complicated." Investigators interviewed by CenterWatch confirmed the difficulties in accessing the CMS database.

"I have not been able to sign in to view what is listed under my name as a PI before it became public," said a Florida-based investigator, who has conducted clinical research for more than three decades. The investigator asked not to be named. When trying to log onto the site during the review period this year, the investigator repeatedly got the message: *No results found. Please refine your search criteria*

Top five companies reporting Sunshine Act research payments in 2015

Total payments in $U.S. millions



Source: Centers for Medicare & Medicaid Services Open Payment Report

and try again. "According to the site, I don't exist," he said.

The AMA and other groups have said the inability of physicians to review their individual data calls into question the accuracy of the information published. In a peer-reviewed article published earlier this year in *The American Journal of Medicine*, the authors found a "concerning level of disagreement" between disclosures reported by cardiologists and pharmaceutical companies about past payments made. Other clinical research professionals have experienced similar findings.

Most investigators, however, don't think it's worth the time and effort to review and challenge inaccurate payment information published about them. According to public CMS data, in program year 2014, less than 5% of physicians registered to review and dispute their data. When the Open Payments submissions process began, leadership in the physicians group of Association of Clinical Research Professionals (ACRP) distributed an internal memo to its members recommending that they consider ignoring the Open Payments dispute process, even if they disagreed with the payment amount, since it would be difficult to find the time or have access to an auditable paper trail that would allow them to win a dispute with a sponsor company over payment amounts.

"There is no easy mechanism for me to review the information. Information is reported about me without my involvement or consent, and the dispute process is unattainable. The companies don't have to listen to you. If you disagree with the amount, they will still publish it. Physicians are actually powerless," said Koren.

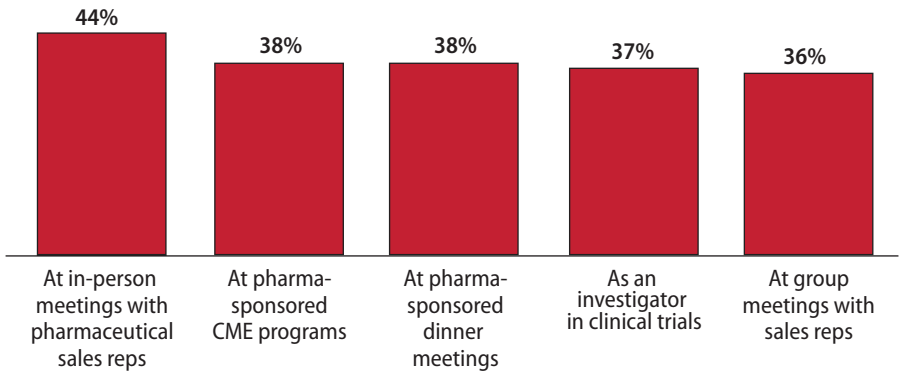
Sponsor companies have set up internal dispute resolutions processes during the past few years, yet organizations also report challenges when investigating individual transactions and resolving disputes within a sponsor's 15-day timeframe. In a letter to CMS, PhRMA said resolving disputed transactions "is likely to be a complicated process" and settling most individual disputes would take several weeks.

Robyn S. Shapiro, attorney and founder of the Health Sciences Law Group, recommends that companies share payment information with investigators in advance, before the 45-day review period begins, to give both sides more time to work out any discrepancies before the information is published.

"There is a maximum of 60 days under the rule to try and work out disagreements. It's not that much time," said Shapiro. "If it's not worked out, the government is just going to report the initial amount. That can not only be wrong, but that can adversely affect the relationship between the industry sponsor and the recipient or site."

Reported impact of the Sunshine Act on physician behavior

Percent of physicians say 'Substantially Less' or 'Somewhat Less' participation



Source: ISR Reports 2014

Discouraging physicians from research

The Open Payments program was meant to address concerns that industry payments to doctors could directly or indirectly affect their scientific independence and clinical judgement; the information is intended to allow consumers to make better healthcare decisions. Yet many fear that public misperceptions about the clinical research payments could have the unintended consequence of causing physicians to exit research and discouraging others from becoming involved in the first place.

According to 2015 financial data, which was posted in June, almost $4 billion of the $7.5 billion in reported payments to physicians and teaching hospitals was for research.

Funding for research projects or studies are reported separately from other general "transfers of value" to physicians, such as lunches or consulting fees, on the publicly accessible website. Yet many have criticized the research-payment reporting as misleading since the amount includes the entire research grant and attributes it to the PI. The payment amount includes study costs such as expenses for overhead, clinical support staff salaries, participant stipends, ethics board fees, advertising costs and subcontracted services required by the research, such as diagnostic imaging, lab work and supplies; PIs receive

only a fraction, if any, of the money. For physicians who work in a medical school or hospital and receive industry grants, the funds reported under their names are typically turned over to the organization and are not a part of their salary.

"There are real concerns about how much the public understands that payment. In parallel fashion, there are concerns by the doctors that people are going to associate all of that as money they put in their pockets," said Shapiro.

Shapiro said some sponsor companies and PIs publish information on their websites explaining the Open Payments Act, why the information is published and how the research grant funds are spent in order to put the research payment in context. Yet many clinical research professionals are concerned that the way Open Payments reports clinical research grants will negatively impact the willingness of physicians to conduct clinical trials.

"There are doctors who don't want the hassle. It's another problem that dissuades people from participating in research. We need more doctors participating in research, so why would you want to make it more difficult for doctors to participate?" asked Koren.

Clinical research professionals have mixed views on the degree to which the Open Payments legislation has negatively impacted the clinical research enterprise since the public database became available two years ago.

DrugDev's Thiede agreed that the overall impact of Open Payments on investigative sites, while clearly an increased burden, has not been as onerous as many originally anticipated, especially regarding the potential for misunderstanding the clinical research grant amounts received by the PIs.

"The feared reaction does not appear to be happening, as there has not been a public outcry regarding what has been made available through the Open Payments reporting," he said. "Thus, I believe physicians who have shied away from clinical trials will reengage as they gain confidence that this reporting will not be misinterpreted and put an unfair light on them."

Yet in a 2014 survey of 173 U.S.-based physicians about the impact of Open Payments on physician behavior, Industry Standard Research (ISR) found that since the enactment of the law, 37% of respondents said their participation level in clinical research dropped. Similarly, in a previous survey, ISR found that one in eight (13%) of investigators would stop participating in some studies if their site started to make "too much" money from clinical trials.

Looking ahead

Over the course of the next three years, more focus on educational and awareness programs about the implications of Open Payments are expected to help improve investigative site compliance with contractual requirements and reduce associated burdens. Sites also will increasingly look for technology solutions that integrate compliance-oriented processes into their clinical operations.

The impact of the legislation on physician willingness to participate in clinical research will depend, in part, on the level of public attention the Open Payments processes receive. While the prospect of additional regulatory requirements already has resulted in some investigators leaving the enterprise or reducing their participation levels, the long-term impact on physician participation in research remains uncertain.

About CenterWatch

For over 20 years, CenterWatch has been the recognized global leader in providing clinical trials information to a broad and influential spectrum of clinical research professionals ranging from top sponsors and CROs to research sites and niche providers, as well as an engaged population of patients interested in clinical research and volunteering.

As a pioneer in publishing clinical trials information, CenterWatch was the first web site to publish detailed information about clinical trials that could be freely accessed by patients and their advocates. Today, we have the largest online database of actively recruiting, industry-sponsored clinical trials.

Visit CenterWatch.com, call (617) 948-5100 or email customerservice@centerwatch.com for more in-depth information on the wide variety of products and services CenterWatch offers.

CenterWatch product and service offerings:

- Periodicals and Business News
- Clinical Study Lead Notification and Site Identification Services
- Market Research and Drug Intelligence Services
- Patient Enrollment Support
- Patient Education
- Career Services
- Clinical Research Training Guides
- Regulatory Compliance
- Content Licensing
- Business Development and Partnership Opportunities

PERIODICALS AND BUSINESS NEWS

The CenterWatch Monthly

The CenterWatch Monthly, the flagship publication, has been a leader in reporting hard-hitting market news and forecasting and analyzing the trends impacting the current and future clinical research landscape. Every issue provides readers with unparalleled, data-rich market knowledge, including clinical study leads and detailed drug pipeline analysis, to help you better navigate and anticipate a changing landscape and assist you in gaining a competitive advantage for greater success.

CWWeekly

CWWeekly provides expanded analysis on the week's top business and financial news along with proprietary access to new clinical study leads, informative conversations with clinical research executives, practical tips for patient recruitment and insightful strategies on study conduct, technology and global trial issues.

Research Practitioner

This bi-monthly journal is a valuable, educational and career advancement resource providing diverse and comprehensive articles that go beyond what staff "should do" and teaches them "how to" incorporate critical concepts and strategies to more effectively manage and execute clinical trials—all while earning valuable nursing contact hours accepted by organizations such as ACRP, CCIP and SoCRA.

CenterWatch News Online

CenterWatch News Online is a dynamic and easy-to-navigate online service featuring real-time objective news reports covering timely stories and emerging trends in the global clinical research industry. Features include: breaking news and top headlines as selected by the CenterWatch editorial staff, news beats featuring relevant content on various industry segments, original feature articles and proprietary CenterWatch data.

CLINICAL STUDY LEAD NOTIFICATION AND SITE IDENTIFICATION SERVICES

TrialWatch for Sites

A complimentary clinical study lead notification service designed to help research centers easily connect with sponsors and CROs seeking qualified investigators for upcoming or ongoing active trials. Sites complete a brief online profile that is stored in a database and then matched against requests from sponsors and CROs. When a match is found, the site information is forwarded to the requesting company for consideration. Site profiles can be completed at centerwatch.com/trialwatch_signup.

TrialWatch for Sponsors and CROs

A complimentary site identification service that helps companies quickly and effectively identify active and experienced investigative sites worldwide to conduct upcoming and active phase I through phase IV clinical trials. Confidential requests can be submitted online at centerwatch.com/clinical-trials/trialwatch.

Research Center Profile Pages

Research Center Profile Pages are an easy and cost-effective way for investigative sites to showcase detailed information on CenterWatch.com about their site offerings and staff expertise and certifications to generate new clinical research study leads , secure contracts and increase their site's exposure to the sponsor and CRO community. Profile Pages are online marketing brochures completely customizable and can include logos, images, video presentations, links to company documents and more. Subscribers can also post unlimited clinical trial listings to assist with patient enrollment initiatives at no additional cost.

MARKET AND DRUG INTELLIGENCE SERVICES

Custom Market Research Services

Since 1994, CenterWatch has been a leader in reporting hard-hitting market news and forecasting and analyzing the trends impacting the current and future clinical research landscape. Our sound journalistic integrity and unmatched market knowledge combined with rich, proprietary data and global contacts gives CenterWatch a unique and objective position in the market to provide invaluable, custom surveys and reports for competitive and market analysis.

Our comprehensive offerings focus on all aspects of the life sciences and clinical trials industry and include primary and secondary data analysis, interviews, focus group research and a broad range of custom surveys such as study performance and relationship feedback surveys, operational efficiencies analysis, drug intelligence and clinical trial activity analysis, outsourcing and new vendor evaluations, site feasibility services and more.

Collaborative Assessment Tool (CAT)

The Collaborative Assessment Tool (CAT) program is a service designed to help CROs and Sponsors routinely gather targeted study-specific feedback and insights from their investigative sites after study completion. CAT is a unique, validated online assessment tool that assists sponsors in identifying opportunities to improve their relationships and optimize clinical trial performance based on 60 initial variables and 29 independent relationship attributes.

Clinical Trials Data Library

The Clinical Trials Data Library provides immediate access to rich and compelling clinical research data and industry statistics to create dynamic, data-driven conference presentations, strategic business and marketing reports, financial plans or to study current and historical activity for training and roundtable discussions.

Data and statistics are derived from several industry sources including proprietary, CenterWatch-conducted surveys with slides ranging from analysis of global economic trends and clinical research practices to examinations of partnerships and drug development pipelines and performance. Charts can be conveniently downloaded, copied and pasted into PowerPoint or Word documents. New volumes available each year.

Drugs in Clinical Trials Database

With more than **5,200** new detailed drug profiles in hundreds of disease conditions worldwide, the Drugs in Clinical Trials Database is an easy-to-search, comprehensive and cost-effective resource that is ideal for industry professionals seeking to monitor the performance of drugs in the pipeline, track competitors' development activity, identify development partners and new clinical study leads or analyze drug information for investment opportunities.

PATIENT ENROLLMENT SUPPORT

Clinical Trials Listing Service™

CenterWatch's Clinical Trials Listing Service™ is the leading online resource for patients interested in clinical trial participation having reached more than 25 million potential study volunteers since launching in 1994. Today, with **80,000+** global listings and a range of exclusive outreach efforts designed to maximize traffic to your clinical trial listings, CenterWatch continues to be a valuable and important addition to any patient enrollment strategy. Sponsors, CROs and research centers can also post trial-specific web ads for additional exposure.

PATIENT EDUCATION

Volunteering for a Clinical Trial

An easy-to-read, IRB-approved brochure designed as a quick reference guide for potential volunteers interested in participating in a clinical trial. It includes an overview of the clinical trials process and answers some of the most commonly asked questions about volunteering. Translations available in Spanish, French, Italian, Portuguese, Dutch and German.

Understanding the Informed Consent Process

A comprehensive, IRB-approved brochure providing study volunteers with important information regarding the informed consent process, including facts and information about the volunteer's "Bill of Rights." Translation available in Spanish.

CAREER SERVICES

JobWatch

JobWatch is an online career and educational resource dedicated to clinical research professionals.

For job seekers: view and apply for open positions, post your resume and cover letter and find upcoming networking events, training or academic degree programs for career advancement.

For employers: with thousands of monthly visitors and exclusive outreach efforts to drive traffic directly to online job postings, employers have an opportunity to reach a highly targeted and engaged clinical research professional audience via a range of tools, including candidate searches, company profiles, web advertising and more. Email jobwatch@centerwatch.com.

CLINICAL RESEARCH TRAINING GUIDES

CenterWatch's training guide series are comprehensive educational resources focused on improving clinical research management skills to conduct safer, more efficient clinical trials.

These guides are perfect for professionals of all skill levels or as a valuable resource for any internal training program or academic curriculum.

- The Principal Investigator's Guide to Conducting Clinical Research
- The CRA's Guide to Monitoring Clinical Research, 4th Ed.
- The CRC's Guide to Coordinating Clinical Research, 3rd Ed.
- Protecting Study Volunteers in Research, 4th Ed.

REGULATORY COMPLIANCE

Standard Operating Procedures for the Conduct of Clinical Research (Electronic and Binder options)

This SOP is developed for investigative sites seeking to comply with the latest FDA regulations and ICH GCP guidelines and to help sites better address organization-specific requirements, implement critical procedures to ensure clinical trial integrity and patient safety, and prepare for random agency inspections. The customizable template includes study management materials, evaluation forms, job descriptions, checklists and detailed procedures.

Standard Operating Procedures for Good Clinical Practice by Sponsors of Clinical Trials (Electronic and Binder options)

The industry's SOP solution to aid Sponsor and CRO organizations in implementing essential policies and procedures to comply with all federal and international regulations and good clinical practices to ensure the conduct of safe, effective and successful clinical trials. Thirty-one (31) SOPs and 82 accompanying forms covering nine sections from general administration, clinical protocol development, study startup to risk-based monitoring, CAPA plan information, quality assurance, and much more.

Standard Operating Procedures for Good Clinical Practice by Sponsors of Medical Device Clinical Trials (Electronic and Binder options)

The only medical device SOP solution that offers best practices while addressing the latest FDA Guidance documents and current device regulations to minimize your organization's regulatory exposure and comply with industry standards. The SOP includes streamlined processes eliminating non-essential, non-regulatory business steps and is completely customizable for immediate integration into your company's operations.

CONTENT LICENSING

CenterWatch offers licensing of our database-driven and static-text content to provide companies with the latest in scientific clinical trial activity and drug development information using market intelligence and knowledge resources. Content can be offered as data feeds and co-branded to seamlessly integrate with a company's web site or Intranet.

Our offerings include:

- Drugs in Clinical Trials Database
- Recently Approved Drugs by the FDA
- New Medical Therapies™
- Patient Education
- Clinical Research Training Guides
- Research Center Profile Pages

BUSINESS DEVELOPMENT AND PARTNERSHIP OPPORTUNITIES

Industry Provider Profile Pages

Industry Provider Profile Pages create online visibility for contract and niche service providers to showcase their products and services on CenterWatch.com to the clinical trials community making it a useful and cost-effective way for providers to generate new business leads, increase exposure and reach a captive and targeted audience. Profile Pages are online marketing brochures completely customizable and can include images and links to video presentations, demos and company documents.

Partnership Opportunities

CenterWatch has developed numerous partnerships and professional relationships with sponsors, CROs, health associations, niche providers and other organizations to better provide the clinical research community and patients with access to the most current and relevant industry, educational and patient-related information possible.

As market research experts, we also collaborate with organizations on various custom projects to conduct both broad and targeted industry-related surveys and to provide detailed data analysis about the clinical research industry. For more information, visit centerwatch.com/about-centerwatch/partnerships.aspx.