HOME STUDY TEST

Earn 3.0 Continuing Education Credits

This test expires on April 30, 2018

(original release date: 4/1/2017)

In this issue of *Clinical Researcher*, the three articles that follow this page have been selected as the basis for a Home Study test that contains 30 questions. For your convenience, the articles and questions are provided in print as well as online (members only) in the form of a PDF. This activity is anticipated to take three hours.

Answers must be submitted using the electronic answer form online (members only, $60). Those who answer 80% of the questions correctly will receive an electronic statement of credit by e-mail within 24 hours. Those who do not pass can retake the test for no additional fee.

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OPINION:

DATA – The Foundation of Clinical Trials

PEER REVIEWED | Richard Young

[DOI: 10.14524/CR-17-0003]

A changing world brings data to the forefront, but how do we manage it all to make the biggest impact?

The life sciences industry has been fundamentally altered in recent years. Diseases that were once considered life threatening and terminal are now being managed as chronic conditions. Previous chronic illnesses are treatable and curable, while other diseases have been reduced to irritations or consigned to the history books.

Clearly, there is much to celebrate, but there is still much to do. Advanced solutions are needed to treat such conditions as multiple cancers, heart disease, obesity, Alzheimer's, and Parkinson's, to name a few. The speed of innovation and the acceleration of new solutions to market will be increasingly important.

Within pharmaceutical companies, the quest for understanding has accelerated, leading to the establishment of a knowledge-based economy with data as the currency. The more we know, the more we can develop these advanced solutions to not only meet, but get ahead of expectations.

Scientific breakthroughs will continue the more we understand the human body—not just the biochemical pathways, systems, and organs, but also the inter- and intrapersonal behaviors that form our very makeup. This process will accumulate vast quantities of data, especially in clinical trials.

As the volume of clinical data rises, the ability to turn those data into quick decisions is limited by today's technology approaches, including electronic data capture (EDC) systems. Consequently, sponsors and sites are not equipped to support new and innovative trial designs, such as adaptive clinical trials.

Making complete and accurate data available will enable life sciences researchers to finally run the trials they want, not the trials today's EDC systems allow. If clinical researchers can have their data in real time, the life sciences industry can better address the problems that are leading to distress, illness, and even death. It is the accumulation and conversion of these data into actionable insights that will drive the era of personalized or precision medicine.

Major Shifts Impacting the Industry

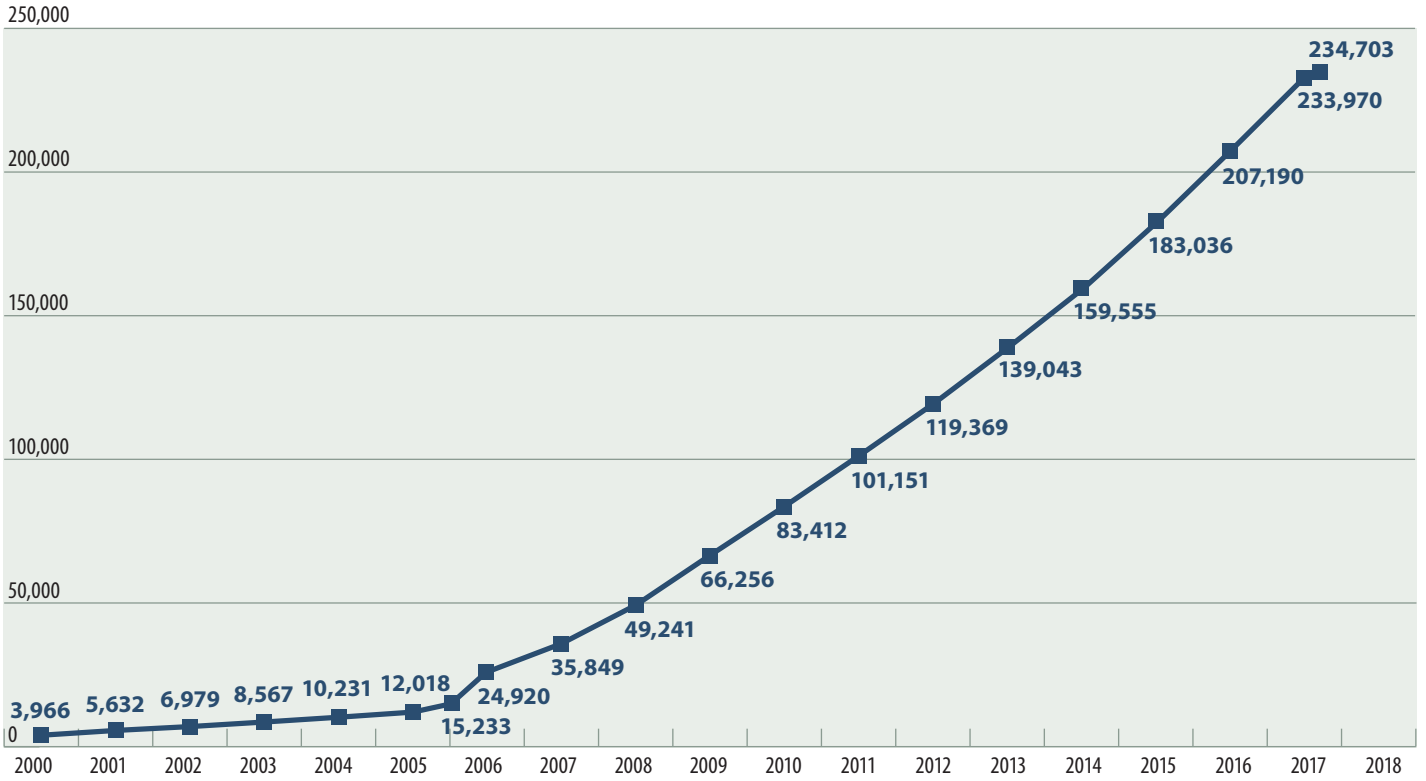
THE RISE OF PERSONALIZED MEDICINE

The industry has long discussed the end of the blockbuster era, which raises the impending need for life sciences companies to find avenues for bringing products to market other than through a narrow focus on potential mega-selling therapies.

LEARNING OBJECTIVE
After reading this article, participants will be able to discuss the importance of turning raw data into actionable insights and decisions for patients in the medical development industry.

DISCLOSURES
Richard Young:
Nothing to disclose

FIGURE 1: Number of Studies Registered with FDA Over Time (as of January 17, 2017)



Source: U.S. Food and Drug Administration (FDA)

In January 2017, ClinicalTrials.gov showed that since 2014, the number of registered clinical studies has increased by almost 50% (see Figure 1). Likewise, new records for U.S. Food and Drug Administration product approvals were consecutively set in 2014 and 2015.

It is easy to conclude that more trials, reaching more patients, and generating more data are resulting in more products to market, but in 2016 that trend was reversed (see Figure 2). This speaks to a rapidly changing environment, and highlights the need for yet more innovation.

Further exacerbating the challenge for manufacturers are looming patent cliffs for many of their top products; in 2016, several high-profile, brand name products were slated to lose patent protection. Patent expirations for highly prescribed medicines will continue to influence healthcare spending as lower cost generics are allowed to compete in the larger marketplace and drive down costs. Although it depends on the type of treatment, the average price of a generic can be as much as 85% lower than its patented brand name counterpart.[1] In fact, between 2009 and 2014, more than $120 billion in pharmaceutical sales was lost to patent expirations.[2]

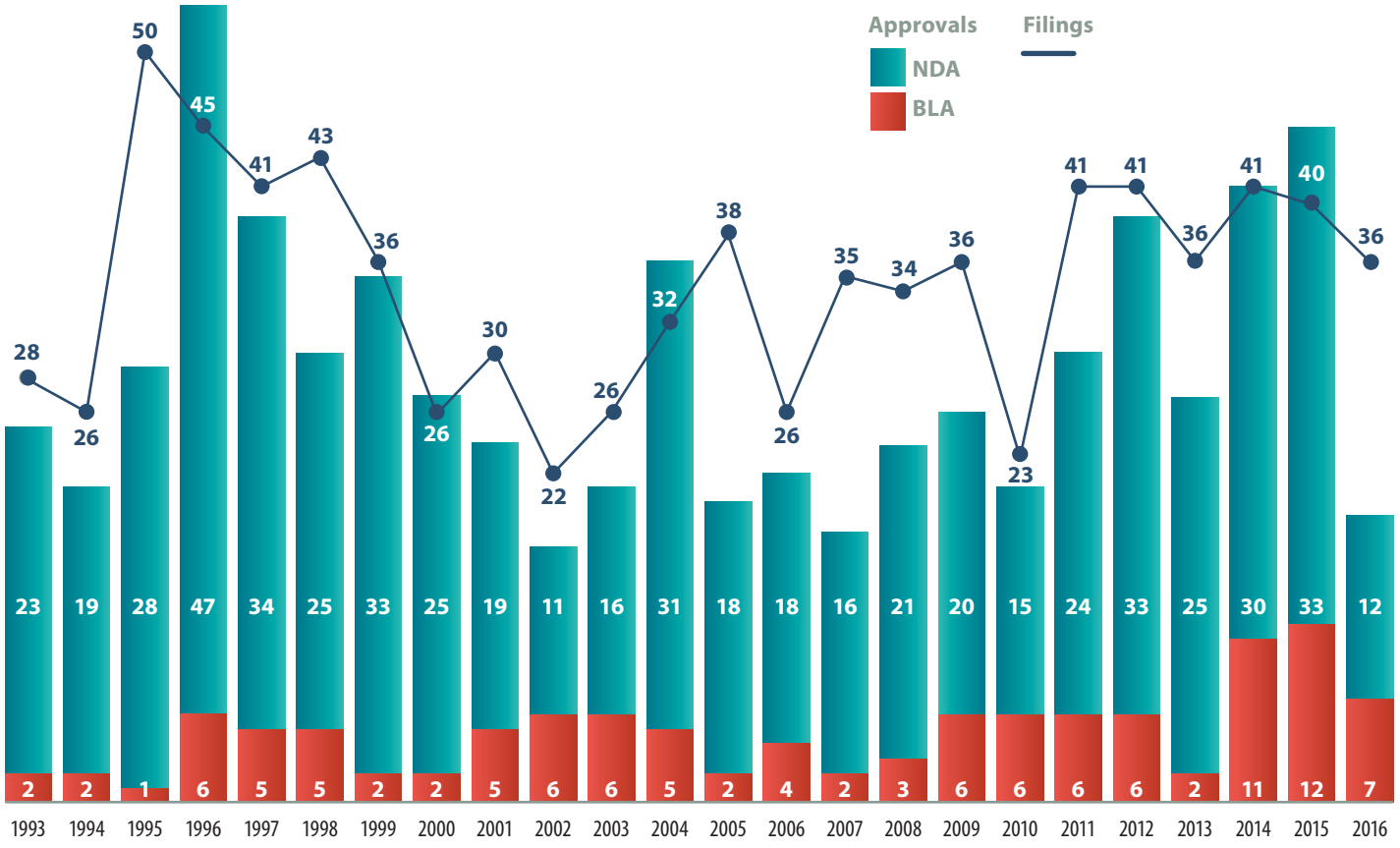
AN INCREASED FOCUS ON PATIENT OUTCOMES

Another major change is linked to consumption models and patients. With every new scientific development, there is renewed expectation of long-term benefit. Armed with heightened anticipation, patients don't buy drugs anymore, they buy outcomes. This means manufacturers will see their reimbursement strategies set on a value-based principle, which depends not only on direct therapeutic effect, but also on patient compliance and adherence.

Insights gained from a better understanding of patient behavior will be vitally important—serving not only as validations for, but also playing a key role in, a treatment regimen itself. Exercise, mobility, social interactions, and behavioral patterns will play a greater role in determining whether patients perceive a sense of wellbeing, as opposed to just being told they are getting better. Understanding the mode of action at a chemical level is crucial, but understanding human nature and human behavior is often the key to determining in what situations a new treatment will actually work.

Patient outcomes combine collective and individual experiences, enabling clinicians to fast-track conclusions in the lab into everyday clinical

FIGURE 2: Number of New Drugs Approved by the FDA Compared to the Number of Filings, 1993 to 2016



Source: U.S. Food and Drug Administration

life. Companies will take this even further through accelerations in personalized medicine, recognizing that all human beings are different and that their characteristics, behaviors, and experiences shape wellbeing.

Data Currency in Clinical Trials

While clinical research continues to advance, the demand for better, faster, more effective treatments shows no sign of slowing. The kinds of scientific advancements that once took 10 years to reach the mainstream could soon take less than two years. To sustain this quest for better knowledge and more effective treatments, however, researchers need to better understand myriad *in vivo* and *in vitro* biochemical processes. That means connecting individuals across the globe—from patient to caregiver, from life sciences to healthcare organizations, and beyond—into the regulatory landscape. Data represent the unit of intelligence, currency, and commodity all wrapped into one neat package.

To establish a free-flowing data stream is difficult enough, but data alone do not deliver the end result. Data are ubiquitous and come in a wide range of volumes, varieties, and velocities. To successfully operate in a knowledge-based economy, data must be consumable and available in real time to derive actionable insights.

Today, the medical development industry is investigating the use of wearable devices, such as FitBit, Garmin, and many others—each capable of generating tens of millions of data points daily. Imagine combining those data with real-time observations, clinical assessments, long-term medical histories, financial data, behavioral data, and even social data. Exploring and characterizing patients from so many dimensions would enable clinicians to create a picture of each individual on a macro and micro level, from cradle to grave, from their very genetic beginnings to their current day experiences.

However, the data are not enough, nor is reviewing the data sources in isolation or combining the data into a periodic dataset. Companies will need to create a complete picture of the individual, refreshed every time a new data point is generated or recorded, in order to turn raw data into actionable insights and decisions. A direct line must be drawn between decision making and continuous improvement in patient wellbeing.

Pulling together this vision of an individual has another acute benefit. By sharing the outcomes and the characteristics of that individual, the industry can connect caregivers and patients across the globe, adding to the knowledge pool and advancing research in unimaginable ways. By mining data confidently, companies can find patterns and draw conclusions that have always evaded researchers until the very end of a clinical study, enabling real-time course corrections that reduce exposure to unnecessary treatments and redirect efforts to the best options available.

In parallel with clinical results, companies will also be able to seek operational patterns and identify problems, challenges, and obstacles faster. Many clinical trials still rely on manual, paper-based, or obsolete systems to collect, manage, and report clinical trial data. Time from event to analysis is still measured in weeks and months, when the need is for minutes and seconds. The application of first-generation eClinical platforms has been heralded as a big achievement, but these efforts have yet to accelerate clinical research or reduce the costs of research in any significant way.

In order to achieve a state of complete and concurrent data—with data equaling knowledge and knowledge leading to better decisions—data should be managed with a single software platform that empowers participants to optimize their contributions in the data value chain. The platform needs to create a coherent and contiguous environment for management of patient data, enabling research in all of its formats, through all of the contributors and consumers of those data.

A Better Way is Needed

EDC systems were first introduced 40 years ago for clinical data management, but really took off at the turn of the century. However, today's EDC is arguable still not a central, critical part of the clinical trial process. More often than not, clinical investigators still turn to paper and pen before EDC; while clinical trials are getting increasingly more complicated, technology is not being leveraged to simplify this complexity. If anything, it is common to find investigators bypass technology completely in favor of manual data capture and then input the data into EDC systems as an afterthought. Does this actually render today's EDC as unfit for purpose?

Let's explore that last question for a few moments, and consider the following stumbling blocks to widespread EDC adoption and making it core to clinical trials:

E for Electronic: Many EDC solutions are still reliant on the traditional paper-based processes, and most patient visits are recorded using paper and pen. These manual steps expose the entire clinical trial process to unnecessary risk and inefficiency.

D for Data: EDC Solutions are really electronic case report form (eCRF) tools that fail to address total data needs. In fact, eCRF data can easily represent less than 20% of study data, according to various estimates.

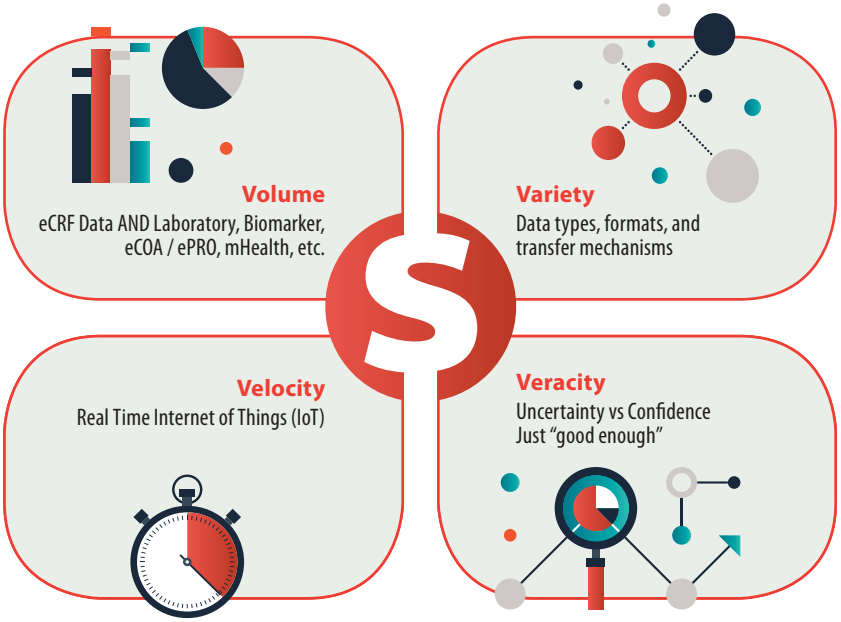
C for Capture: If all your EDC solution does is enable data capture, what about data management, monitoring, and reporting?

For clinical trial solutions to be classed as "fit-for-purpose," all of the incoming data must first be accessible in real-time and in one place. This provides a complete and concurrent view of data that is very specific to every patient, effectively creating a patient passport. A real-time window into patients' own worlds can deliver a better understanding of their symptoms, behaviors, and actions. Consolidating data not only advances the patient cause, but also improves the likelihood of success. Trials become faster, better informed, more knowledgeable, and better placed to react to whatever events arise.

Armed with heightened anticipation, patients don't buy drugs anymore, they buy outcomes. This means manufacturers will see their reimbursement strategies set on a value-based principle, which depends not only on direct therapeutic effect, but also on patient compliance and adherence.

Within pharmaceutical companies, the quest for understanding has accelerated, leading to the establishment of a knowledge-based economy with data as the currency. The more we know, the more we can develop these advanced solutions to not only meet, but get ahead of expectations.

FIGURE 3: Finding the Value in Data



To be fit for purpose, a data management tool (perhaps EDC) needs to address each and every data type plus the "four Vs" of data (see Figure 3):

- **Volume:** Managing vast quantities of data (structured and unstructured) without system performance degradation or financial loss. Today's EDC and eCRF solutions are designed to just manage data entered at the site, which is typically just a fraction of the total data in a study, according to various estimates.
- **Variety:** Managing data from a variety of sources, in differing formats and data types. Many EDC or eCRF solutions are designed to manage structured data, in limited format types.
- **Velocity:** Managing data in real time and consuming and supplying data with simplicity and elegance. EDC or eCRF solutions often are not designed to handle large volumes of data, so adding significant volumes causes severe performance delays.
- **Veracity:** Recognizing that not all data are born equal and that different strategies may be required for each data point (in essence, a risk-based data strategy). EDC and eCRF solutions are designed to manage data by type, and therefore need external assistance to drive more varied strategies.

Advanced, fit-for-purpose EDC solutions will address the needs for volume, variety, velocity, and veracity, and will lead to a full value assessment that aids study design, execution, and conclusion.

By mining data confidently, companies can find patterns and draw conclusions that have always evaded researchers until the very end of a clinical study, enabling real-time course corrections that reduce exposure to unnecessary treatments and redirect efforts to the best options available.

Realizing the Clinical Trials of the Future, Today

The life sciences industry will, very soon, be able to eliminate the need for paper in a clinical trial setting. However, companies need to not just eliminate paper, but completely redefine user experiences to be *paperless*—electronic systems will no longer be designed to look and behave as pieces of paper. This will result in user interfaces that are far more intuitive and that have advanced functionality, such as search and automatic grouping, designed into the system.

Real progress will also come from tackling data at the source. More often than not, source data are still recorded on paper manually with a pen or a paper-like format (using Microsoft Excel or Word). The resultant need for source data verification has a significant negative impact on the ability to reduce trial time or cost, and has been subject to many recent reviews that highlight only minimal quality advances.

As patients record more of their own data, paper is still the preferred solution. This only exacerbates and extends traditional challenges. For example, the "car park syndrome" is well documented, with patients who forget to fill out their diaries or questionnaires trying to recreate their experiences and symptoms as they sit in their cars just before they walk in to see their doctors. If company leaders tackle the source data challenge correctly, they not only advance clinical research, they also create a path to better, faster, long-term medical records that facilitate data sharing across multiple solutions (i.e., EDC and electronic health records).

While cloud-based technology and Big Data management have delivered proven results across the board in all industries, the life sciences industry has been slow to adopt a true cloud-based solution capable of delivering on global usage, minimizing costs, and handling data. Mainly, this is due to the lack of a true cloud solution that addresses these issues to date; when software doesn't work, it makes routine tasks and processes more difficult.

The Next Wave of Innovation in Clinical Data Management

Clinical trials are a very patient-centric, patient-driven process. Someday soon, patients will have complete control of their data. Personalized medicine is designed to ensure that our research delivers medical solutions that are better defined and that increase an individual's likelihood of responding. To understand individuals, each patient must

be closely examined, including through the use of data that haven't yet been considered for clinical trials. The true fit-for-purpose EDC solution will handle all of the data a patient can generate, and use those data to derive real-time decisions for patients and caregivers.

Clinical research can become truly global, connecting patients and caregivers across the globe. This opens up new vistas for clinical data capture and management to bring the trial to the patient. The Internet-of-things (the interconnection via the Internet of computing devices embedded in everyday objects, enabling them to send and receive data), for example, has increased the ability for data to be shared in real time and opened up the possibility of integrated data from varied sources flowing into clinical trial management. With it, the industry can take clinical research to previously improbable, if not impossible, places. Consider, for instance, rather than sites finding only patients who live or can temporarily stay nearby, how it may soon be a routine situation in which patients can remotely find trials based anywhere through smart devices and the experimental drugs can be administered and monitored from thousands of miles away.

Further, while succeeding quickly is a critical goal, failing early in trials is also vitally important for both financial and patient wellbeing reasons. Not every new clinical solution will drive benefit, therefore, there is opportunity to redirect money, resources, and patients.

Cloud computing, mobile health technology, Big Data, and the Internet of things hold immense potential when it comes to transforming clinical trials, especially ones that span geographic boundaries. A global, cloud-based solution for clinical data management makes installation, ongoing maintenance, and performance inherently easy, while managing cost, time, and resources. The true, fit-for-purpose EDC solution will work anywhere, anytime, and enable life science companies to design and execute the trial that they want, not the trial that is limited by technology today.

As important, this type of Internet-enabled cloud solution will increasingly support a global economy, including emerging and developing countries where 54% of adults identified themselves as Internet users in 2015.[3] Of course, the digital divide remains a challenge, but as more tech giants like Google (with its "Project Loon" initiative) and Facebook (with its "Internet.org" initiative) drive innovations forward to bring the Internet to more people, this challenge will slowly, but certainly, diminish.[4]

Conclusion

The life sciences industry is at an inflection point where the drive for patients, treatments, and research is increasingly global, medicine is becoming personalized, and there is a growing demand for new drugs to reach the market faster. With these trends in mind, a true cloud-based clinical data management solution that delivers global clinical trials and incorporates a high variety, volume, and velocity of data into personalized clinical trials is needed. This system will go far beyond the EDC solutions of today, which have not delivered on innovation in well over a decade, as well as beyond the eCRF limitations that have historically governed clinical trial processes. Clinical trials are still largely paper-based undertakings, and EDC systems serve largely as data entry systems.

The next generation of EDC solutions will combine data from every source in real time, present those data to all consumers, and facilitate clinical trials. This will mean embedding technology across the clinical trials process—from patient to regulator—ensuring that every observation, result, and event is captured as it occurs. Currently it is typical for data to be recorded on paper first and entered many days later. Ideally, however, data will be digitized at the source precisely when a patient event is happening, anywhere in the world, at any time, and will become a part of the global dataset immediately, not days or weeks later. Learning, patient management, and ability to address challenges will all happen in real time.

Technology will not only support the clinical trial, but the wider healthcare systems, feeding data into the patient's long-term medical records. The benefits of harmonizing across life sciences and healthcare will reap huge rewards, and will ultimately save the need for some research altogether. Still, the life sciences industry has a long way to go when it comes to leveraging technology to transform clinical data management. Industry is moving fast toward digitalizing clinical trials on a global scale, and the life sciences companies that are not quick to ride this change will soon be left behind with insurmountable costs, unable to keep up with the changing economy.

To change clinical research is to change patients' lives, and the power to do this comes from encouraging fresh innovations and identifying the barriers that stop our advancement. Data and knowledge help us to learn, and it is through learning that we can make real change.

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Ensuring Compliance with Part 11: *A Site's Perspective*

PEER REVIEWED | Cristina Ferrazzano Yaussy, MPH, CCRP | James Wetzel

[DOI: 10.14524/CR-17-0005]

Today's clinical research sites are under tremendous pressure to produce more in an increasingly complex environment; however, the sophistication of sites' information technology (IT) systems often remains antiquated, lagging those used by the healthcare organizations with which they work. Office bookshelves bursting with paper binders function better as cubicle walls than workable repositories. Manual processes limit credentialed staff from realizing potential, and siloed systems and departments prevent productive collaboration.

In this environment, as more sites are looking to implement technology to go paperless, improve standardization, and provide secure access to essential documents, site staff's experience with ensuring compliance with 21 CFR 11 (Part 11) of the *Code of Federal Regulations*—focusing on the U.S. Food and Drug Administration's (FDA's) standards for electronic records and electronic signatures—may be limited. Balancing the need to maximize efficiency and ensure compliance presents a challenge, but with the right resources, the challenge is an achievable one. Gaining a better understanding of the purpose, scope, and components of Part 11 will help sites achieve their compliance goals.

Understanding Part 11: Purpose & Scope

In light of the Paper Reduction Act of 1995, the FDA aimed to rid itself of inefficiencies in record keeping. Recognizing the value of computer systems, yet the need to balance the security, authenticity, and reliability of electronic records, the FDA set forth to define regulations that would allow for the use of electronic records in the agency's mission. Thus, Part 11 was released in 1997.

Part 11 plays a vital role in the larger purpose of the FDA. By ensuring the security, authenticity, and reliability of data collected during a trial—and the systems that manage and process those data—the agency aims to ensure the safety and protection of the public.

Much debate has ensued over the applicability of the regulation, largely due to a lack of understanding. Essentially, Part 11 applies to any organization engaged in FDA-regulated research that maintains records electronically. This includes any records in electronic form, whether created, modified, maintained, archived, retrieved, or transmitted to others.[1] The general rule is that if a record is sent to the FDA or is required by the FDA to be maintained, and is managed electronically (electronically signed, disseminated, stored, etc.), it falls under the regulation.

Understanding Part 11: Five Components

Developing a process for Part 11 compliance at a research site can be a good thing. More often than not, it becomes an opportunity to look at the site's internal processes, the state of its standard operating procedures (SOPs), the presence or lack of a quality management system, and its ability to entertain inspections and audits. Furthermore, addressing the expectations of Part 11 thoroughly better prepares a site for the technologies of tomorrow.

The development of a site's Part 11 compliance process can be broken down to five main components, as described in the following sections.

Define Policies and Procedures

The first step to building out a Part 11–compliant process is to have a solid foundation and appropriate guidance, policies, and SOPs.[1] SOPs demonstrate

LEARNING OBJECTIVE
After reading this article, participants should be able to understand and identify critical components related to 21 CFR 11 compliance and how to implement and maintain an effective compliance process.

DISCLOSURES
Cristina Ferrazzano Yaussy, MPH, CCRP;
James Wetzel:
Nothing to disclose

a commitment to quality and reinforce the operational practices that a site upholds. They also serve as a resource for training staff, so that research teams understand their roles in following procedures and maintaining compliance with Part 11.

As a best practice, sites should maintain a portfolio of SOPs (see Table 1). This will help facilitate a consistent approach to implementing technology and safeguard against any potential oversights of the critical components of Part 11.

When moving to a document management system, sites should determine in advance which record(s) will be maintained in electronic format and document this decision in an SOP. Should a sponsor, monitor, or auditor inquire about such procedures, a well-developed SOP will ease their concerns.

System Functionality Review

When selecting a system to manage electronic documents and signatures, sites should conduct a thorough review, as specific functionality is required under Part 11 (see Table 2). This review should not be limited to the minimum required functionality, such as audit trails and authority checks; sites should use this as an opportunity to evaluate how the system can impact other site operational areas.

Consider, for example, the general auditability and configurability of the system. Does the system provide advanced keyword search functionality, so that documents are easily retrieved by staff or reviewers who are unfamiliar with naming conventions or file structures? Inadequate accessibility or retrievability can impede the auditing process, which could lead to inspection findings. Furthermore, files that are organized, secure, and readily accessible will improve overall staff efficiency.

Can the system be configured or modified by administrators without requiring time-consuming revalidation? For example, you hire a new regulatory specialist and need to modify the system to allow access to regulatory documents, but not financial documents. A well-designed system can accommodate these types of administrative changes without requiring revalidation (explored further below). Furthermore, it will help a site to accommodate growth without needing to rely on the vendor for every modification.

Site leaders will want to decide if they desire a system with advanced access functions that allow administrators to control whether certain users can upload and edit documents, but others only to view and sign those same documents (or not see them at all). Robust access controls and permissions can allow for a more controlled, yet more collaborative team.

While the software manufacturer can provide guidance in this review, it is the responsibility of the site to conduct and document a review of the system's functionality as it relates to Part 11. Use the system review as an opportunity to learn how the system can impact overall efficiency and usability.

Vendor Selection: Finding the Right Partner

Similar to an FDA inspection of a site, a site's evaluation of a vendor provides insight into the vendor's development and quality management processes. As vendors are entrusted with site data, site leaders should ensure they have adequate controls in place to prevent issues and handle exceptions.

Furthermore, auditing a vendor facilitates constructive dialogue between the site and vendor,

TABLE 1: EXAMPLES OF STANDARD OPERATING PROCEDURES (SOPS)

SOP	Description
SOP Development and Maintenance	Outlines the process by which all other SOPs are developed, approved, and maintained
Vendor Selection/ Audit	Outlines the procedures of performing vendor audits to ensure software providers are selected based on their capability to provide quality software and documentation for system validation
Records Management	Outlines how and by whom documents will be managed, including matters related to certified copies, retention, and accessibility
Software Implementation and Maintenance	Outlines initial validation, user acceptance testing (UAT), ongoing maintenance, and change control procedures
Electronic Signature Policy	Attests that users understand that their electronic signature holds them accountable; a letter of Non-Repudiation Agreement for digital signatures must be submitted to the FDA prior to change[3]
Training	Ensures users have adequate training and agree to terms of using the system

TABLE 2: CRITICAL COMPONENTS OF PART 11 FUNCTIONALITY

System Feature	Part 11 Compliant Application
Electronic Records Management	• System designed for electronic records management and functions as designed • Records are available for export and review throughout the retention period • Workflow follows sequential steps and prevents nonsequential actions
Audit Trail	• Automatic tracking of changes to electronic records • Date and time stamp for all actions and changes • Audit trail available for review and export throughout retention period
Security	• Access controls based on user role or permissions • Prevention of unauthorized access • Alerting of unauthorized access attempts • Secure access/password reset methods
Electronic Signatures	• Automatic tracking of name, date, time, and Statement of Testament associated with signature • Viewable and exportable manifestation of eSignature with Statements of Testament • Executing and linking the signature to the underlying record • Signatures cannot be attached to other record or removed

Balancing the need to maximize efficiency and ensure compliance presents a challenge, but with the right resources, the challenge is an achievable one. Gaining a better understanding of the purpose, scope, and components of Part 11 will help sites achieve their compliance goals.

which can lead to improvements in product quality. Poor development practices can lead to performance issues resulting in lost time (e.g., recovering information) and money (e.g., to purchase another system), damage to data integrity, and exposure to gaps in compliance with Part 11 or SOPs.

Sites should review the vendor's SOPs related to training practices, servers, records retention, disaster recovery, and software development/validation. This will provide insight into the vendor's development practices, as well as its understanding of the requirements of Part 11.

Evaluating the vendor's implementation and software release (or update) process is also important, as this will play a key role in ongoing maintenance and stability of the system. System updates are necessary for ongoing security and functionality improvements. However, if updates are released hastily or without adequate notice from the vendor, a site may be unprepared to perform adequate testing or training. Conversely, if updates are infrequent, desired improvements in functionality will not be met and known problems or "bugs" can perpetuate unreliable records.

If a site has an IT department, that department's staff should be involved in the process from the very beginning. Not only will they provide insight from a technology perspective, but they may also need to work closely with the vendor to ensure their procedures or requirements can be met. Sites without dedicated IT support should look for a vendor that provides additional assistance.

Sites should also closely review the level of support the vendor will provide for training and ongoing validation. Without adequate support, a site will need to plan for additional time and expertise in these areas. In the larger sense, a vendor that is knowledgeable and dedicated to Part 11 compliance can function more as a partner by ensuring a smooth transition and long-term success.

Validation

The process of performing and documenting systematic testing (validation) of the system is also a critical component of compliance with Part 11. In the same manner a car manufacturer may conduct a crash test to ensure the airbags work, sites must test their systems to ensure they function reliably. As we increasingly trust systems to perform tasks, we must ensure they perform them correctly.

While validation can be a complex chore, industry trends point to an increased focus in this area. In fact, the November 2016 revisions to the International Council for Harmonization's (ICH) Guideline for Good Clinical Practice E6 (R2) specifically require that computer systems be validated.[2] This requirement was developed to offset sites' increased reliance on allowing sponsors, contract research organizations (CROs), and vendors to conduct validation on their behalf.

While a qualified and knowledgeable partner can help, ultimately, validation is the responsibility of the site. It is not a one-time occurrence or something that is "covered" by a vendor or sponsor—it is an ongoing process that sites need to own.

To conduct system validation, sites should develop a user acceptance testing (UAT) protocol to systematically evaluate performance. The UAT protocol should outline what the system should do (requirements), how it should do it (specifications), and how testing should be performed to ensure it functions correctly. The results should be documented along with any unusual observations. UAT should be repeated (revalidation) when requirements and specifications relating to Part 11 are modified, which typically happens with a major system update.

Similarly, validation of the infrastructure (hardware) hosting the system must also be conducted. The process may change whether the system is hosted by the site or by the vendor. However, the responsibility of ensuring the integrity of the hardware ultimately falls on the site. When using a vendor, a site is entrusting the protection of its information in the vendor's hands, therefore the site should ensure the hardware being used to host its data is properly validated.

Training

Training is an integral part of selecting and using electronic systems for research projects. The processes surrounding how and when training is conducted and documented is a responsibility of the site that can be made more efficient with assistance from vendors. Simply put, persons who develop, maintain, or use electronic records and electronic signature systems (staff for vendors and the site end-users) must have procedures in place so that they have the proper education, training, and experience to perform their respective tasks.

Training is everyone's responsibility, and is necessary to ensure that the system is used properly and that users can identify when it may not be working correctly. Inadequate training may lead to compliance issues, as data integrity and access controls can be compromised through misuse of a system. Training should be conducted upon implementation and updated along with any major changes to the system that follow.

As an added level of support to sites, and to help promote compliance with Part 11, a system can offer automated training to all individuals upon entry and request that they attest to understanding their responsibilities for documentation purposes. Training should be consistent with the function/responsibility of the end-user, and should be documented along with the eSignature attestation. This attestation is to document that users understand that when they use a system and apply their eSignature, it is equivalent to their hand-written signature, which is a fundamental aspect of Part 11.

Where Do You Start?

So, how do research site staff begin to tackle Part 11, especially if they are questioning if it will even be worth the effort? Besides pleasing an auditor, what benefits will a site realize from compliance with this regulation? Moreover, where does one begin, given the volumes of information about Part 11 that a simple Google search provides?

Some site leaders may even question if, in the event of an FDA inspection, the agency is really going to look at Part 11 compliance—especially given that there have been few if any inspection findings to-date of research sites nonconformance in this area. The concerns are valid, but consider the following: Recent FDA guidance on investigator responsibilities highlights an increased focus on the research site. In fact, the aforementioned ICH E6 (R2) references many of the same concepts outlined in 21 CFR Part 11 as they relate to the investigator's responsibilities for data handling, record keeping, and audit trails. Further, the increased use of technology systems to manage essential documents means these systems are more likely to be looked at closer by auditors and inspectors.

The best place for site leaders and staff to start is to evaluate what they don't know about Part 11. Know when a function falls under compliance and when validation should occur. At a minimum, know that it is not a "task" to be relegated to the IT team, nor is it a product feature to be bought or a box to be checked. While others can certainly help, maintaining compliance is an operational process whose responsibility is shared throughout the site.

Next, take inventory of what needs to be done. One critical question that needs to be asked early on is "What can we improve as a site before, during, and after this compliance effort?" Perhaps new SOPs need to authored? Responsibilities need to be better defined. Online shared drives need to be organized. Make a list.

Next, evaluate how current processes and procedures may be impacted. How might this affect staff onboarding? Does the site have specific training requirements? Does it have specific back-up or retention requirements that are different from what vendors provide?

Also evaluate the capabilities of everyone at the site to carry out these tasks. How will this affect new staff? Is it a large site with a dedicated training or validation team? Or a small site with stretched resources? Take stock of where help may be needed.

There is an abundance of resources at sites' disposal for assisting with complying with 21 CFR Part 11; whitepapers, websites, federal regulations, case studies, vendors, consultants, and even CROs and sponsors can be a resource for learning the steps involved. Do not be afraid to lean on vendors or reach out to CROs and sponsors, but most importantly, find a resource that has successfully navigated these compliance waters.

After the validation and compliance efforts have been completed, understand that it is a journey and not a destination. Documentation of ongoing efforts of compliance, making use of a quality system, documenting and doing what your SOPs say—these are all part of the process.

In summary, then, the following is a high-level view of key considerations for implementing a Part 11 compliance process:

- Perform a self-assessment and gap analysis
- Identify how to fill in the gaps
- Develop policies and procedures
- Find a solution and a knowledgeable partner to fill gaps
- Implement new processes
- Implement and validate the system
- Train your team
- Perform ongoing evaluation and quality assurance

Once site staff have undertaken the process and received feedback on their efforts (hopefully through something other than an FDA Form 483), they will be equipped to apply the process to new technologies that require compliance. Additionally, sponsors and CROs will recognize the site's new-found level of sophistication and be more likely to want to conduct studies at the site.

Conclusion

One of the greatest challenges facing clinical research sites is ensuring regulatory compliance, especially when using technology to manage documentation. While not easy, the journey to compliance can improve the research site in more ways than just in terms of its validation and audit preparedness; it can bring better SOPs, happier staff, and more efficient research conduct.

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Using EHR Data Extraction to Streamline the Clinical Trial Process

PEER REVIEWED

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Since 2005, the average time from approval by the U.S. Food and Drug Administration of an Investigational New Drug application to a New Drug Application approval has been 8.1 years. From 2003 to 2013, the cost to develop an approved new drug has more than doubled from more than $1 billion to nearly $2.6 billion.[1]

Much of the cost and slowness of the overall process is a result of difficulties in recruiting appropriate patient populations. Recent research shows that only 13% of investigative sites exceed their enrollment, and that initial Phase II–IV study timelines are often doubled to reach study enrollment goals.[2] This has resulted in unnecessary protocol amendments that cause delays and dramatically increase costs of developing new therapies.

The three main players in the clinical trial process—biopharmaceutical firms, contract research organizations (CROs), and healthcare organizations—face obstacles as they navigate through the difficult waters of bringing new drugs to market. For instance:

- **Biopharmaceutical firms** lack real-time data, so site selection is often relationship-driven and susceptible to site failures. Clinical investigators are prone to overestimation of patient availability, which leads to under-enrolled study sites. Overly restrictive eligibility criteria, among other trial characteristics, also make some protocols unfeasible.

  Further, protocol amendments pose one of the greatest obstacles to effective clinical trial execution. Amendments are costly, time-consuming solutions to underlying clinical trial issues such as increasingly complex protocol design and difficulty recruiting patients. Nearly two-thirds of protocols require at least one substantial amendment, and a typical protocol ends up with an average of 2.3 amendments. On average, the cost of a single protocol amendment is $453,932 and the total cost for sponsors to implement "avoidable" protocol amendments is nearly $2 billion annually.[3]
- **CROs** are challenged when inclusion/exclusion criteria are chosen without verifying the impact on availability of a cohort, which can create avoidable amendments. The possibility of underbidding the project also increases their risk. CROs strive for competitive differentiation, but the lack of tools to leverage clinical and health-related data can be a barrier to winning more business. CROs endeavor to help their pharma clients develop more pragmatic operational solutions, but require real-world data for better protocol design and feasibility studies.
- **Healthcare organizations** seek to attract more clinical trials—both to generate additional revenue and to help develop new therapies. Unfortunately, competition is increasing for a shrinking pool of National Institutes of Health (NIH) funding and grant funding rates in general are declining. The number of newly registered NIH-funded trials decreased 24% from 2006 to 2014. At the same time, competition from new research areas has increased.[4]

LEARNING OBJECTIVE
After reading this article, participants should be able to discuss the benefits of utilizing EHR technology in planning and conducting clinical trials.

DISCLOSURES
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Employee of TriNetX, Inc.

Increasingly, the answer is to extract real-time patient clinical data residing in healthcare organization electronic health records (EHRs). Leveraging these detailed data allows pharma companies and CROs to identify patients who match exactly the eligibility criteria for the cohort they are seeking.

EHR Data are Key

The traditional clinical trial process is broken. The question is how to utilize technology to optimize the process.

Increasingly, the answer is to extract real-time patient clinical data residing in healthcare organization electronic health records (EHRs). Leveraging these detailed data allows pharma companies and CROs to identify patients who match exactly the eligibility criteria for the cohort they are seeking. EHRs are transactional systems, optimized for capturing and quickly retrieving individual observations about single patients.

Combing through individual records to find groups of patients is something most forms of EHRs do not support well, if at all. The class of software tools designed to identify patient cohorts relies on data extracted from EHRs and transformed to allow nimble cross-patient searching. The data "liberated" from EHRs frequently represent a subset of all available patient information, are typically limited to observations stored as discrete elements, and are therefore easy to extract.

Cohort identification tools use the extracts of data to provide a first pass at defining patient cohorts that match the criteria of interest. These cohorts are "coarse," and require additional refinement. Nonetheless, cohort identification tools eliminate the need to "boil the ocean" to find the specific patients required by significantly narrowing the target population to be reviewed, screened, and eventually enrolled into a trial.

A data-based approach reduces overall site attrition and results in fewer sites with more applicable patients. Ultimately, it will decrease the overall cost and accelerate the development of new drug therapies.

Emerging Enabling Technology

Some providers are already using healthcare information technology (IT) solutions to conduct clinical trial design and site feasibility studies. Although many of these data analytic offerings provide access to large patient populations, these solutions (e.g., data aggregators) are typically based on centralized data sets in single institutions.

For example, the Case Comprehensive Cancer Center at Case Western Reserve University in Cleveland, Ohio has developed an automated tool that matches patients with ongoing clinical trials at the point of care. Using this tool, physicians were able to facilitate patient enrollment in active clinical trials in conjunction with existing clinical workflows.[5] This ability to find the types of patients that exactly meet trial criteria quickly and easily illustrates the benefits of EHR data extraction technology.

Success in single institutions highlights the power of extracting and leveraging EHR data. The key to industry-wide success, however, is expanding this enabling technology to include larger databases collected from multiple healthcare organizations, broadening the scope of data they make available (e.g., biomarkers, imaging, information "locked" in narrative text of notes and reports, etc.), and increasing adoption of these tools across the spectrum of the biopharma research enterprise.

The nearly universal adoption of EHR technology, maturing standards and interoperability, a desire to use accumulating clinical data to improve care delivery, and growing appreciation that data collaboration is ultimately required to realize its full potential have opened the door to the widespread sharing of EHR data that represents the next step in improving the clinical trial process. Up to now, there hasn't been a real-time patient data resource available to help develop protocols and recruit patients. Pharma companies have been forced to use epidemiology data, which are often several years old or worse before being published, and may no longer be relevant.

Technology solutions now allow pharma companies and CROs to access EHR data from healthcare organizations globally on a near real-time basis. Advances have made it possible to study patient data securely. Companies can query de-identified, federated databases to research actual patients by reviewing aggregated EHR-based patient records. They can alter eligibility criteria, instantly see the effect on their overall cohort, and learn whether relevant sites have access to sufficient number of eligible patients. They also can identify problems with inclusion/exclusion criteria earlier during protocol development, significantly reducing the cost and delays caused by protocol amendments.

This new technology protects patient privacy by providing de-identified data during research, then allowing re-identification only after a healthcare organization has agreed to participate in a trial. This greatly improves the recruitment phase of the trial process.

Success in single institutions highlights the power of extracting and leveraging EHR data. The key to industry-wide success, however, is expanding this enabling technology to include larger databases collected from multiple healthcare organizations.

The cost to access a user-friendly EHR platform may strain the budgets of many small pharma companies or CROs, but affordable pricing models are becoming available to address this issue.

A Few Words of Caution

However, while EHR data offer many advantages to clinical research, some downsides exist. Extreme diligence is required to shield sensitive protected health information from cyber breaches, some data types may be missing from a given EMR, and coherent, consistent policies and practices for secondary use of EHR data need to be developed worldwide.

Further, the cost to access a user-friendly EHR platform may strain the budgets of many small pharma companies or CROs, but affordable pricing models are becoming available to address this issue. Despite concerns with EHR usage in clinical research today, the advantages of using this "big data" still outweigh these few current drawbacks.

Mapping Disparate Data to Enable Collaboration

A core element of cohort identification based on federated databases of EHR data is the mapping of disparate clinical data coding standards to a common terminology for ease of use and seamless research collaboration. This eliminates the need for healthcare organizations, pharma companies, and CROs to struggle with translating coding language from multiple systems and organizations.

Clinical data captured by EHRs and extracted for cohort identification is typically coded, meaning that individual data elements are assigned codes from relevant controlled terminology, or coding systems like ICD-10-CM, ICD-10-PCS, and CPT. Some data elements, while coded, are used under different standards at different organizations (i.e., providers of medication standards include Walters Kluwer's Medi-Span, Cerner's Multum, First DataBank, and others).

To provide interoperability, disparately coded data must be mapped to a unified set of standards. The mapping process can be costly, since current standards are at different stages of maturity and have varying levels of support and relevant tooling for mapping. A typical mapping exercise requires extensive manual review by terminology experts to ensure high quality. In addition, every mapping is dynamic, in that the effort requires ongoing maintenance due to changes in both the underlying source data and the target standard terminology.

In short, harmonizing data to a unified set of standard terminologies is a necessary step in enabling the functions of cohort identification tools and is a key feature of the new technology.

Using EHR Data to Avoid Costly Amendments

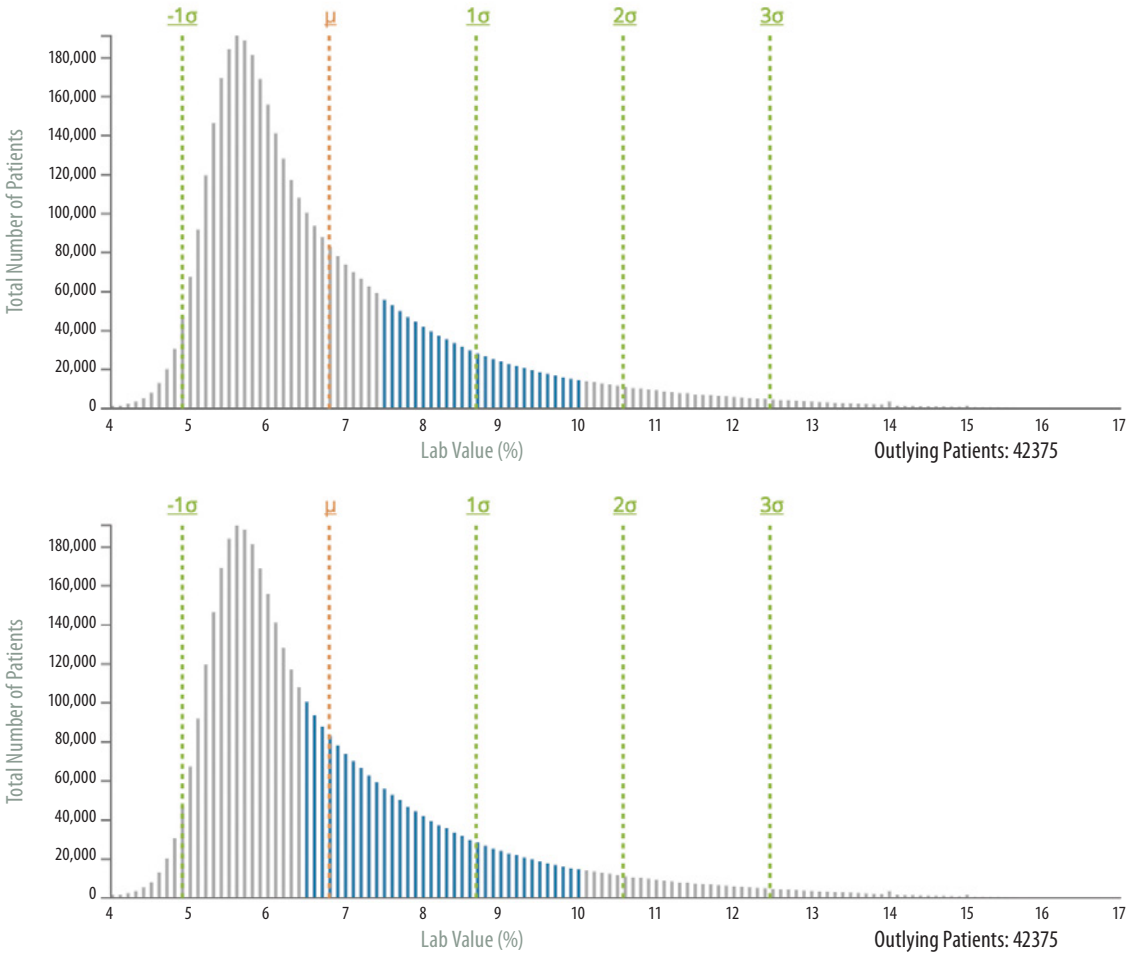
Some organizations have already begun using federated EHR data from multiple healthcare organizations to develop their protocols and recruit patients, and early results are encouraging. Planners, investigators, protocol writers, and strategy teams have been able to move recruitment planning upstream to align with the clinical design process. This has helped to ensure trial feasibility and reduce the number of preventable clinical trial amendments.

ICON, a CRO based in Ireland, was able to leverage EHR data from a global research network to support a bid defense for a European pharmaceutical company. The firm had been initially dropped from consideration, but was later able to become a viable contender because of its use of real-time EHR data.

At the bid defense, ICON presented an HbA1c sensitivity analysis, as the client was contemplating changing the lower range of its protocol from 7.5 to 6.5. Using the cohort identification technology, ICON was able to quickly run the analysis at both 6.5 and 7.5, and found that the difference in the number of matching patients was only 30 for that specific cohort (see Figure 1). Since the cohort already had more than 8,000 matching patients, ICON recommended that the client keep the study entry criterion at 7.5. Another CRO had advised changing the criteria, but the client was hesitant, as its entire program had been based on the 7.5 criterion. The client was pleased that ICON had been able to quickly provide real data from real patients to justify keeping the original higher threshold.

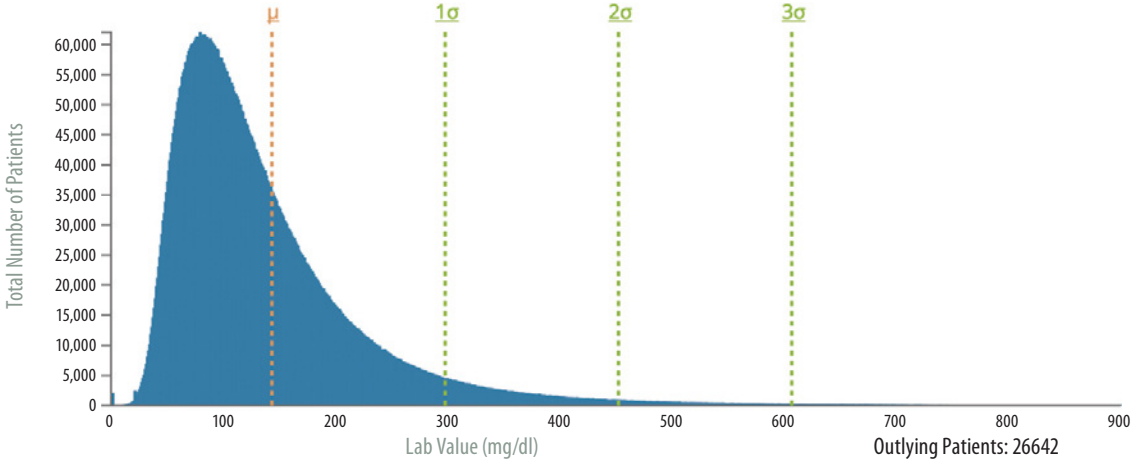
In another case, ICON was able to help a U.S. client determine triglyceride parameters to use as an inclusion criterion for a large cardiovascular trial being planned. In this situation, ICON, again using cohort identification technology, was able to show the full distribution of triglyceride lab results across a large representative population. It then adjusted the upper range so the client could see the effect on the patient population that still met the target cohort size (see Figure 2).

FIGURE 1: HEMOGLOBIN A1c SENSITIVITY ANALYSIS



A comparison of 6.5–10% vs. 7.5–10% HbA1c lab results. While the lab criteria alone yield a larger number of patients for the broader 6.5–10% range, the overall effect of modifying the lower range from 7.5% to 6.5% was negligible (less than 0.4% difference) when applied to the full study inclusion and exclusion requirements.

FIGURE 2: TRIGLYCERIDE LAB



A view of the number of patients according to their most recent triglyceride lab results. The EHR platform allowed the user to enter various value ranges to determine the best-suited triglyceride parameters for inclusion criteria for an upcoming study.

	Min	Max	Median	Mean(μ)	Std. Dev(σ)
Network Stats	0.0	20,957.0	113.00	143.37	154.44

Greater than or equal to mg/dl

Less than or equal to mg/dl

Most Recent Result Ever

FIGURE 3: ORIGINAL VS. EXPANDED AMENDED DISEASE CRITERIA

14,715 Patients
Population 5–17 years/any gender (7,127,901)

	M08 Juvenile arthritis
OR	L93 Lupus erythematosus
OR	M32 Systemic lupus erythematosus
OR	M33 Dermatopolymyositis (juvenile dermatomyositis)
OR	M34 Systemic sclerosis (scleroderma)
OR	M35.0 Sicca syndrome (Sjogren)
OR	M35.1 Other overlap syndromes
OR	M30 Polyarteritis nodosa and related conditions
OR	M31.3 Wegener's granulomatosis
OR	M31.5 Giant cell arteritis with polymyalgia rheumatica
OR	M31.6 Other giant cell arteritis
OR	M31.7 Microscopic polyangitis
OR	M31.4 Aortic arch syndrome (Takayasu)
OR	M30.1 Polyarteritis with lung involvement (Churg-Strauss)
OR	D89.1 Cryoglobulinemia
OR	L95.9 Vasculitis limited to the skin, unspecified
OR	M35.2 Beçhet's disease (Beçhet's syndrome)
OR	K50 Crohn's diseas (regional enteritis)
OR	K51 Ulcerative colitis

EHR technology allows for patient cohort size comparisons based on the addition of several diseases. In this example, an amendment that opened enrollment to patients with cerebral palsy, Duchenne muscular dystrophy, diabetes, celiac disease, or cystic fibrosis in addition to all other prior allowed diseases expanded the number of eligible patients by 72% within the 5–17 year age range based on target indications alone.

53,351 Patients
Population 5–17 years/any gender (7,127,901)

	M08 Juvenile arthritis
OR	L93 Lupus erythematosus
OR	M32 Systemic lupus erythematosus
OR	M33 Dermatopolymyositis (juvenile dermatomyositis)
OR	M34 Systemic sclerosis (scleroderma)
OR	M35.0 Sicca syndrome (Sjogren)
OR	M35.1 Other overlap syndromes
OR	M30 Polyarteritis nodosa and related conditions
OR	M31.3 Wegener's granulomatosis
OR	M31.5 Giant cell arteritis with polymyalgia rheumatica
OR	M31.6 Other giant cell arteritis
OR	M31.7 Microscopic polyangitis
OR	M31.4 Aortic arch syndrome (Takayasu)
OR	M30.1 Polyarteritis with lung involvement (Churg-Strauss)
OR	D89.1 Cryoglobulinemia
OR	L95.9 Vasculitis limited to the skin, unspecified
OR	M35.2 Beçhet's disease (Beçhet's syndrome)
OR	K50 Crohn's diseas (regional enteritis)
OR	K51 Ulcerative colitis
OR	G80 Cerebral palsy
OR	G71.0 Muscular dystrophy (Duchenne)
OR	E08-E13 Diabetes mellitus
OR	K90.0 Celiac disease
OR	E84 Cystic fibrosis

72% increase in eligible patient population

Some organizations have already begun using federated EHR data from multiple healthcare organizations to develop their protocols and recruit patients, and early results are encouraging.

FIGURE 4: ORIGINAL VS. EXPANDED AMENDED FRACTURE CRITERIA

1,018 Patients → 33,896 Patients

	532.0 Fracture of lumbar vertebra	45,596

The pharmaceutical company implemented another amendment to the same trial in order to expand the size of the potential patient population. In looking at only the fracture criteria, the initial inclusion criteria of vertebral fracture only identified 1,018 patients in the specified 5–17 age group, but it was augmented to 33,896 patients when all types of long bone fractures were later added—even with the requirement that they must occur in the prior two years. Our EHR source was able to show that the expansion of fracture criteria alone allowed a 97% increase in potential patients.

Event 2 – All of the terms in this event occurred between today and 24 months ago

	532.0 Fracture of lumbar vertebra	45,596
OR	542.2 Fracture of upper end of humerus	70,808
OR	542.3 Fracture of shaft of humerus	44,674
OR	542.4 Fracture of lower end of humerus	67,734
OR	552 Fracture of forearm	213,988
OR	572 Fracture of femur	92,469
OR	582.1 Fracture of upper end of tibia	44,436
OR	582.2 Fracture of shaft of tibia	65,717
OR	582.3 Fracture of lower end of tibia	28,856
OR	582.4 Fracture of shaft of fibula	58,482

FIGURE 5: ORIGINAL VS. FULLY AMENDED PROTOCOL CRITERIA ANALYSIS

20,513,595 – 18 sites	**Network**	20,513,595 – 18 sites
3,823,331 – 18 sites	**Population – Ages 5–17**	3,823,331 – 18 sites
8,565 – 17 sites	**Inclusion Criteria Diseases** *(plus all other remaining criteria)*	48,772 – 17 sites
2 – 1 site	**Allowed Fracture Types**	615 – 15 sites
0 – 0 sites	**Glucocorticoid Requirement**	38 – 7 sites

Using analytical tools available in our EHR source allows for comparison of the complete original (pre-amendment) protocol vs. the most current protocol (after several amendments). While the size of the EHR network and patients within the 5–17 age range remain the same in the top portion of both funnels, the impact of specific parameters—diseases allowed, types of fractures allowed, medication requirement—can be clearly noted in the resulting patient numbers. At the same time, the effect of all protocol criteria together can be considered. Here we are able to show that there were no potential patients who met the non-amended protocol criteria, while the fully amended protocol was broadened enough to identify 38 patients.

"Being able to use cohort identification technology based on EHR data provides us with the objective data and analytics on real patients to help our clients make decisions that matter," said Otis Johnson, PhD, MPA, vice president for feasibility and clinical informatics at ICON.

In an example of the technology's ability to drive in-depth portfolio planning, a leading pharma company was able to leverage a multisite federated EHR database to evaluate a long-standing inclusion screening criterion that was perceived to be hampering recruiting efforts. Using data extraction to research a larger population of quantitative data, the company was able to see from side-by-side comparisons with and without the criterion how it changed the eligible patient number. The company then removed the criterion from the protocol template, which improved the potential patient pool and recruitment efficiency to potentially avoid costly amendments.

Another global healthcare company using the traditional site and patient selection process ended up with five amendments over an eight-year period and enrolled a total of 23 patients. The initial protocol wasn't able to enroll a single patient. The study manager felt this would be the case, but had no tangible data at that time to dispute key opinion leaders who insisted there would be patients.

A retrospective analysis revealed how each amendment expanded the potential patient pool and delivered a collective assessment to the updated eligibility criteria overall. A final assessment that took all existing criteria and the five amendments into consideration and drew on EHR data from multiple healthcare organizations yielded 38 potential subjects. A similar analysis of the original protocol found zero patients—the same findings of the actual study before any amendments were considered.

As of the writing of this article, the trial has 23 patients enrolled, supporting the findings in the analysis and demonstrating the viability of EHR data analytics in "stress testing" a protocol for feasibility from conception to avoid costly amendments upstream (see Figures 3–5).

EHR Data–Based Results Match Epidemiologic Findings

The value of EHR-based studies has furthermore been validated in terms of ability to reproduce epidemiologic findings published in medical literature. EHR-based data extraction can provide a proactive method of producing accurately defined patient populations. This allows healthcare organizations, biopharma companies, and CROs to make better, more timely decisions.

Conclusion

Developing new therapies and getting them to market is cumbersome, time consuming, and costly. Flawed protocol design based on anecdote or opinions often fail to find the right patients for trials. Site selection based on art instead of real-world data is fraught with risks of trials closing due to failure to accrue patients. Cohort identification technology based on EHR data provides a better way.

The industry now has a treasure trove of real-time, relevant information in the form of EHR data being collected from nearly every healthcare organization. The key is getting to that information and leveraging it to make better upfront decisions and streamline the clinical trial process.

Along with the emergence of a culture of data sharing that improves availability of data for research, advances in data interoperability and maturing technologies for federated databases and cloud and data analytics are now allowing healthcare organizations, pharma companies, and CROs to tap into a vast wealth of data. As use of these collaborative networks increases, EHR data will soon become the key building block on which the industry can build a more effective, efficient process to bring new therapies to market faster. Eventually, that will lead to better clinical outcomes, which represent everyone's ultimate goal.

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HOME STUDY HS

Technology for Trials

OPEN BOOK TEST

This test expires on April 30, 2018

(original release date: 4/1/2017)

OPINION: Data—The Foundation of Clinical Trials

1. **According to the author, which of the following will accumulate vast quantities of data, especially in clinical trials?**

- **A.** Reviewing data from long-completed studies and repeating those studies in new populations.
- **B.** Regulatory expectations that all data from human subjects be deposited with ClinicalTrials.gov.
- **C.** Increased use of personal fitness wearable devices by healthy persons enrolled as controls in studies.
- **D.** A greater understanding of the structures and behaviors that make up the human body.

2. **Recent patent expirations on top pharmaceutical products have led to which of the following?**

- **A.** A nearly 400% increase in the number of firms producing generic drugs since 2010.
- **B.** A loss of more than $120 billion in sales across a five-year period.
- **C.** Record numbers of patients being hospitalized due to use of prescription drugs for off-label purposes.
- **D.** A spike in adverse event reports from doctors seeing patients who've taken expired medicines.

3. **According to the author, what is required to turn raw data into actionable insights and decisions?**

- **A.** Data storage capacities that are unavailable to all but the largest pharmaceutical firms.
- **B.** Committees of reviewers representing both internal and external stakeholders.
- **C.** A complete picture of a patient, refreshed whenever new data points occur.
- **D.** Electronic data capture (EDC) systems with expanded capabilities that are still under development in the U.S.

4. **When were EDC systems first introduced?**

- **A.** 10 years ago
- **B.** 20 years ago
- **C.** 30 years ago
- **D.** 40 years ago

5. **Electronic case report form (eCRF) data are estimated to represent how much of total study data?**

- **A.** Less than 20%
- **B.** Nearly 30%
- **C.** More than 40%
- **D.** Exactly 50%

6. **What is necessary for clinical trial solutions to be classed as "fit for purpose"?**

- **A.** Data must be collected without error.
- **B.** Auditing must take place prior to entry into an EDC tool.
- **C.** All incoming data must first be accessible in real time and in one place.
- **D.** Outgoing data should have had two audits to ensure accuracy of source data.

7. **As described in the article in relation to data management tools, "variety" of data involves which of the following?**

- **A.** How expensive the data are to collect and mine.
- **B.** How many people involved in the study are allowed to input data.
- **C.** When to use risk-based strategies for collecting the data.
- **D.** What formats, sources, and types the data arrive in.

8. **How does source data collection using the paper format affect trials?**

- **A.** Increases time and costs due to need for source data verification.
- **B.** Decreases time and costs due to less equipment being required.
- **C.** Increases patient drop-out rates due to the "car park syndrome."
- **D.** Decreases site staff workload due to allowing the trial to close sooner.

9. **Which of the following happens when paper is used as the answer to data capture?**

- **A.** It provides ease of monitoring and auditing.
- **B.** It exacerbates and extends traditional data challenges.
- **C.** It reduces the need for usernames and passwords.
- **D.** It increases the likelihood of protecting data privacy.

10. **Personalized medicine is designed to do which of the following?**

- **A.** Ensure that research delivers medical solutions that increase an individual's likelihood of responding.
- **B.** Allow patients to choose what providers and procedures they would like to involve in their care.
- **C.** Streamline delivery of similar treatments across culturally similar patients with the same conditions.
- **D.** Cure patients of their diseases through the shortest and least expensive courses of treatment possible.

Ensuring Compliance with Part 11: A Site's Perspective

11. **Who must comply with 21 CFR 11 (Part 11)?**

- **A.** Only industry sponsors of clinical trials, as they are responsible for and initiate the clinical investigation.
- **B.** Any organization engaged in U.S. Food and Drug Administration (FDA)-regulated research that maintains records electronically.
- **C.** Any healthcare provider, including doctors and staff of clinics, hospitals, nursing homes, and pharmacies.
- **D.** Healthcare providers who conduct financial and administrative transactions electronically.

12. **Part 11 applies to which of the following types of records?**

- **A.** Only those that are sent to sponsors so that trial results may be published.
- **B.** Those that detail why a drug candidate was not approved for marketing.
- **C.** Records that are sent to FDA or required to be maintained by the FDA.
- **D.** All budget and contract records associated with the clinical trial.

13. **What are the key components for establishing Part 11 compliance?**

1. Establish site policies and processes
2. Evaluate the system functionality and audit the vendor
3. Validate the system and train all users
4. Obtain FDA approval for the system

- **A.** 1, 2, and 3 only
- **B.** 1, 2, and 4 only
- **C.** 1, 3, and 4 only
- **D.** 2, 3, and 4 only

14. **In selecting a Part 11–compliant vendor, which services should be provided for optimal success?**

- **A.** Initial system training for super users and fee-for-service support package.
- **B.** Ongoing training for all stakeholders and ongoing Part 11 validation support.
- **C.** A Part 11–ready system with a user manual and no additional support.
- **D.** Off-the-shelf system with suggestions for using the system.

Find the most current online test at **www.acrpnet.org/homestudy**, including any revisions made after publication of this issue of *Clinical Researcher*.

15. **What is necessary for system validation?**

A. Vendor-provided documentation that the system is compliant is all that is necessary.

B. Test driving the system once by randomly checking various components to determine that it is usable.

C. Approval by the FDA indicating that the system is acceptable and in compliance with Part 11.

D. Initial and ongoing systematic testing of the system by the site to confirm that it is functioning as intended.

16. **Which of the following statements are true regarding training requirements for Part 11 compliance?**

1. Training should only be performed upon system implementation.

2. Training should be consistent with the function/responsibility of the end-user.

3. The processes surrounding how and when training is conducted and documented is a responsibility of the site.

4. The processes surrounding how and when training is conducted and documented is a responsibility of the vendor or sponsor.

A. 1 and 3 only

B. 1 and 4 only

C. 2 and 3 only

D. 2 and 4 only

17. **When evaluating site standard operating procedures (SOPs), which SOPs are necessary to support the requirements of Part 11?**

1. Vendor selection/audit

2. Records management

3. CRF quality assurance

4. Electronic signature policy

A. 1, 2, and 3 only

B. 1, 2, and 4 only

C. 1, 3, and 4 only

D. 2, 3, and 4 only

18. **What are the key system features of a Part 11–compliant system?**

1. Integration with FDA gateway

2. Records available for export and review throughout the retention period

3. Automatic tracking of changes to electronic records

4. Automatic tracking of name, date, time, and Statement of Testament associated with signature

A. 1, 2, and 3 only

B. 1, 2, and 4 only

C. 1, 3, and 4 only

D. 2, 3, and 4 only

19. **A review of a Part 11–compliant system's features and functions that a site will use is the responsibility of which of the following?**

A. The sponsor

B. The site

C. The vendor

D. A combined effort

20. **When should training on a Part 11–compliant system be performed?**

A. Only upon implementation

B. Only when major system changes occur

C. Upon implementation and annually

D. Upon implementation and with any major changes

Using EHR Data Extraction to Streamline the Clinical Trial Process

21. **Extracting real-time patient data through EHR technology allows a sponsor to ultimately do which of the following?**

1. Accelerate trial timelines

2. Identify cohorts of subjects eligible for a study

3. Qualify investigators

4. Lower costs

A. 1, 2, and 3 only

B. 1, 2, and 4 only

C. 1, 3, and 4 only

D. 2, 3, and 4 only

22. **What will the universal adoption of EHR technology require?**

A. Enhanced protected health information (PHI) data security

B. A combination of public and private grants and funding

C. Patient consent

D. Larger datasets from multiple healthcare organizations

23. **What has the Case Comprehensive Cancer Center done with its automated EHR tool?**

A. Recruit patients for upcoming clinical trials

B. Allow physicians to match their patients with active clinical trials

C. Assist investigators with protocol design

D. Match physicians to patients

24. **What aspect of EHR technology greatly improves the recruitment stage of a clinical study?**

A. Re-identification of a patient only after a healthcare organization has agreed to participate in a trial

B. Re-identification of a patient before a healthcare organization has agreed to participate in a trial

C. Re-identification of a patient during research

D. Re-identification of a patient at any time

25. **Which of the following are current drawbacks to utilizing EHR technology?**

1. Missing data

2. PHI protection and security

3. Lack of policies regarding secondary use of the data

4. No affordable access options for small pharmaceutical firms/contract research organizations

A. 1, 2, and 3 only

B. 1, 2, and 4 only

C. 1, 3, and 4 only

D. 2, 3, and 4 only

26. **"Mapping clinical data" refers to what?**

A. Tracing disparate clinical data back to each patient's electronic medical record

B. Applying searchable codes to a dataset

C. Conducting an extensive manual review of clinical data and unifying the data to a standard terminology

D. Ongoing data maintenance by institutional review board experts

27. **What was ICON able to achieve by leveraging EHR data?**

A. Provide real-world data to support a broader range for HbA1c lab eligibility criteria

B. Identify an alternative lab to replace HbA1c

C. Construct data-driven recommendation to not change the minimum value for a lab eligibility criteria

D. Find 30 additional patients to recruit into the study

28. **What was the retrospective analysis using EHR data assessments able to prove?**

A. Some amendments could have been avoided by upfront protocol feasibility testing.

B. Cohort size comparisons were not always useful.

C. EHR analytics provided to a key opinion leader were highly influential in the leader's decision making.

D. Cohort identification technology identified 23 potential subjects to enroll.

29. **EHR data have been validated for representativeness and reproducibility of what?**

A. Insurance claims

B. Socioeconomic status

C. Epidemiologic findings

D. Risk-based monitoring needs

30. **Which of the following are future benefits of leveraging EHR data?**

1. Improved clinical outcomes

2. Getting new therapies to market faster

3. Cost savings

4. Investigator motivation

A. 1, 2, and 3 only

B. 1, 2, and 4 only

C. 1, 3, and 4 only

D. 2, 3, and 4 only