The Clinical Research Regulatory Process

Understanding the Impact

A CenterWatch-Complion Survey

by Rick Arlow, Founder and CEO Complion Inc.

Introduction

The importance of data validity obtained from a clinical research trial including the conduct of that trial, and site operations, cannot be overstated. That importance was the motivation and rationale for a CenterWatch survey study, commissioned by Complion late in 2014, of over 160 sites and medical centers -- and a wide range of individuals -- to better understand the regulatory process and the impact on sites. The efforts of this study sought to quantify the regulatory burden on these sites by identifying key metrics, and identify opportunities for improvement. This document provides an overview and analysis of the results of that survey study.

Background: The Increasing Regulatory Burden

One of the initial CenterWatch study findings revealed that 85% of sites reported an increased regulatory burden, as compared to just two years ago. Separate studies by other organizations have provided background, and revealed interesting data on the impact of regulatory process.

For instance, a Tufts Center study spanned over a six-year period, 1999-2005, found substantial increases in the following areas: Inclusion Criteria, CRF Length, Trial Duration, and Adverse Events.

Regulatory Requirements	Level of Increase
Inclusion Criteria	3x
CRF Length	2.3x
Trial Duration	1.7x
Adverse Events	1.2x
Severe Adverse Events	12x

Tufts Center CSDD Study 1999-2005

In addition, Protocol Complexity has shown continued growth, driven by sponsors' desire for more procedures in their trials, which often results in an increased work burden for sites.

Another study, conducted by the Tufts Center for Drug Development, examined work burden growth reported by sites over a ten-year period. This study found the increase of work burden to be consistent with the increase in the number of procedures. Ultimately leading to the increase of regulatory burden, given the elevated risk of deviations, violations, and amendments.

Protocol Complexity	Level of Increase Over 10 Years
Work Burden	73%
Total Procedures	64%

Tufts CSDD 2013; N=2,671 protocols

Shifting Site Responsibilities

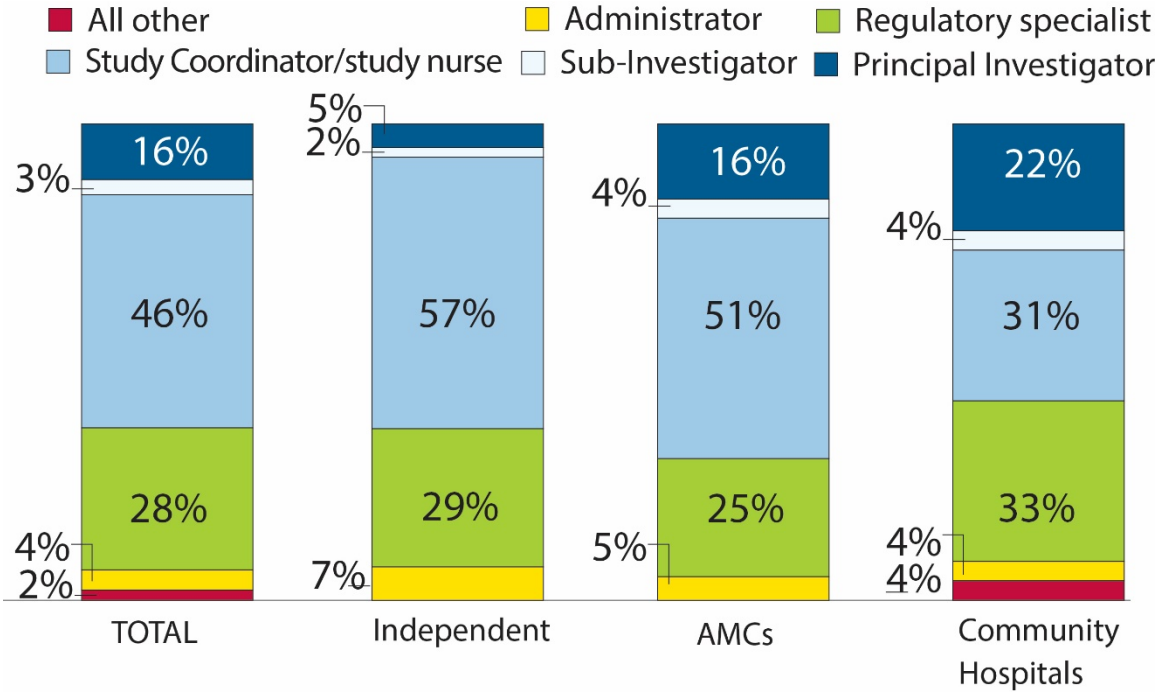
In the past sites would receive documents primarily via FedEx. These documents would arrive prepackaged in binders. But anecdotal evidence suggests that over the last several years sites are increasingly receiving study information via email. In order to accommodate existing paper-based processes and infrastructure, sites must print out the emails and store the hard copies -- in addition to managing them by sorting through and filing the emails.

Anecdotal evidence suggests another significant trend, as many sites shift from onsite to remote monitoring. Monitors increasingly request access to site records and regulatory files in between on site visits. This can lead to a bigger burden on the research site as the need to locate and provide that information to the sponsor continues to increase. That process can be further complicated by turnover among monitors and staff.

That's the background on the regulatory environment and the direct impact on sites. The next section dives into specific data from our survey.

Survey Overview

Primary Manager of Regulatory Compliance Tasks

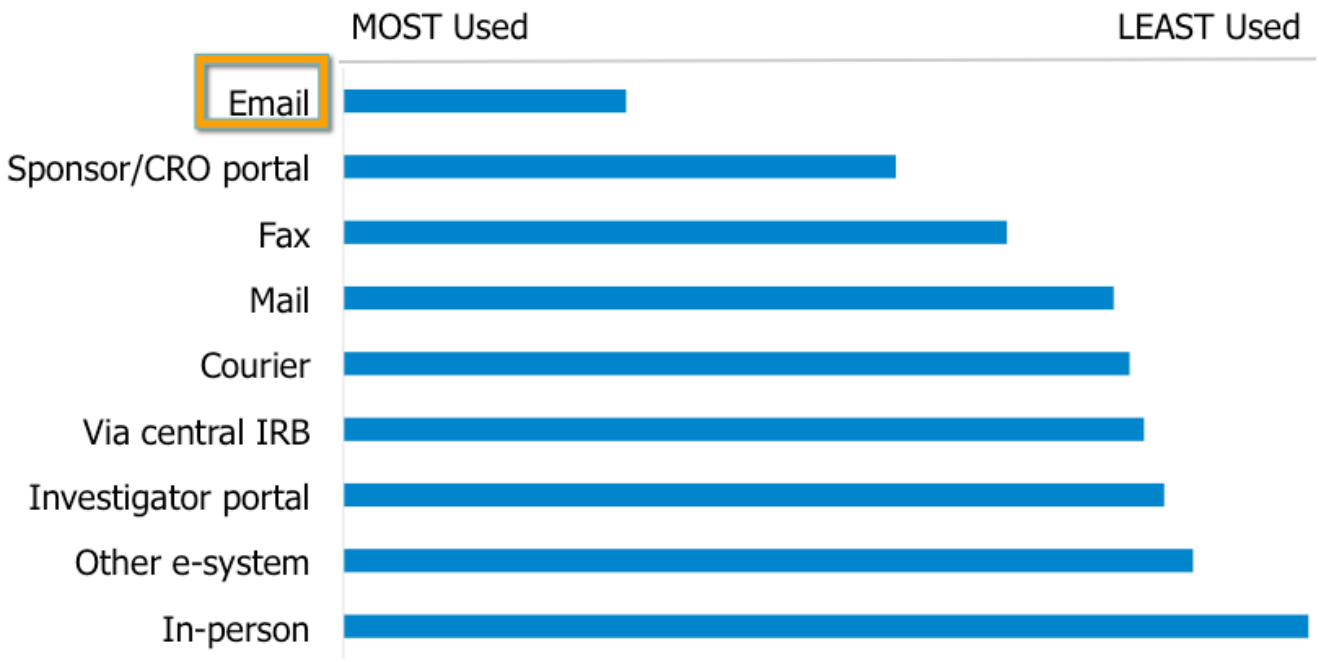


Source: CenterWatch Complion Study, 2015; N=164 Investigative Sites

One of the objectives of CenterWatch-Complion Site Regulatory Survey was to identify which roles within the surveyed organizations act as the primary manager of regulatory compliance.

Our survey found that in most situations the main responsibility for managing regulatory compliance falls on the study coordinator or the research nurse. In community hospitals there may be a higher percentage of individuals that are regulatory specialists, and some independent research centers and sites may have a dedicated regulatory manager. But in many cases it may not be feasible to have a full-time person specifically focused on regulatory compliance. In such cases there may be multiple people involved, primarily study coordinators who spend the majority of their time focusing on patient care and other operational activities that directly impact the research study.

Exchange of Regulatory Information



Source: CenterWatch-Complion Study, 2015; N=164 Investigative Sites

Our survey also explored how regulatory information is delivered from the sponsor or the CRO to the site. In the graphic above, the shorter the blue line, the more often that method of information exchange is used. As you can see, the survey data indicates that email is by far the most common form of exchange of regulatory information, including start-up and other documents and ongoing correspondence. The second most common means of information exchange is via a portal provided by the sponsor or CRO. The evidence is clear that most regulatory information is exchanged through electronic means. But how is that information being stored?

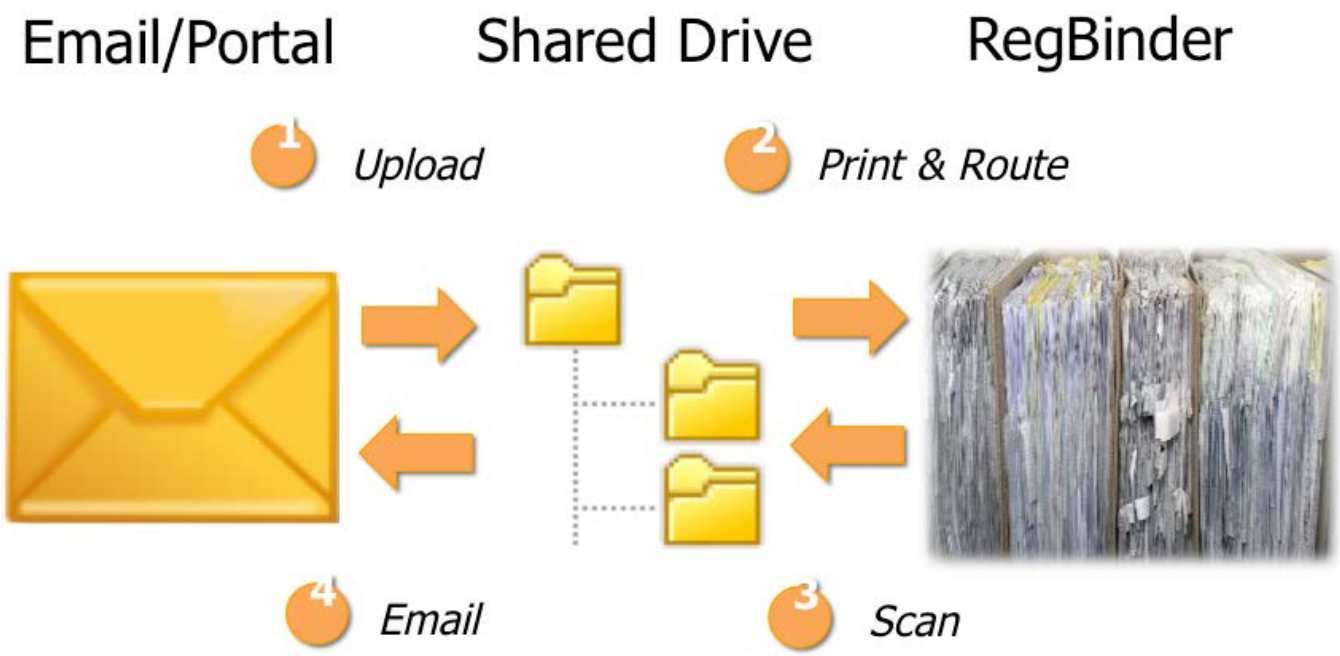
Storage of Regulatory Information

> We've been told for years that we are in a paperless environment, but you'd never know it by the size of our regulatory documents.

While regulatory information at the sponsor, CRO, and site levels is increasingly being transmitted electronically, many regulatory documents remain stored in a paper-based environment. The vast majority of the respondents to our survey, 81%, reported using a hybrid method for storing regulatory documents.

Hybrid Regulatory Process

In a hybrid process, information received electronically (via email, portal, etc.) is stored in some type of shared drive, either on the local network or on some other system to which stakeholders have access. However, the FDA has specific regulations, 21 CFR Part 11, that establish requirements for maintaining electronic records and utilizing electronic signatures. Often the shared drives involved in these hybrid systems do not meet the FDA requirements governing the access and the security of the information stored on these drives.



Since most electronic systems do not meet the FDA requirements, sites practicing this hybrid approach must print out paper copies of the documents and maintain them in approved regulatory binders. In some cases situations may arise when off-site monitors or the CRO need access to the authorized information, the paper documents must be scanned once again in order to be transmitted electronically.

Clearly, this is not the most efficient approach.

Metrics and Benchmarks

Among of the most interesting concepts to emerge from this study are the high-level metrics on the amount of information and documentation that is actually being stored. Over one half of survey respondents reported receiving between 250 to 500 correspondences, typically via email, over the duration of a clinical trial. That information was then stored as hard copies, totalling about 500 pages or 4 physical binders, which are then archived for approximately 11 years. Considering that research site conduct multiple, concurrent trials, the amount of paper and the number of binders multiply. The physical volume of information consumes a significant amount of office space, 15% to 25% or more on average.

Operational Metric or Benchmark	#	n
Correspondence exchanged	251-500 Or more	158
Binders used to store regulatory documents	4 binders Or more	160
Pages for all of the regulatory documents	500 pages Or more	155
Years to archive the regulatory documents	11 years Or more	155
Percentage of site's physical office space dedicated to Storage of regulatory documents	15-25% Or more	156
Percentage of sites using third party archiving*	63%	155

Source: CenterWatch-Complion Study 2015

The metrics gathered in the study were fairly consistent across the different types of sites and organizations involved, with one notable exception. In the *Percentage of sites using third party archiving* metric. academic medical centers and community hospitals used third-party archiving for the vast majority of their studies, while private practice and other groups relied more heavily on on-site archiving.

Material Costs Per Study

Cost associated with material	Cost Per Study
Archive / storage	$ 500
Printer ink	$ 100
Shipping*	$ 120
Paper	$ 111
Binders	$ 100
Storage boxes	$ 75
Folders	$ 50
Envelopes	$ 20
Total Actual Material Cost	**$ 1,126**

* To/from storage, interoffice, to sponsor/CRO

Among the various factors associated with materials involved in the creation, management, and storage of physical documents, archiving and storage represent the biggest drain on budgets, averaging $500 per study. As the graphic above indicates, our survey of over 160 different sites revealed an average total materials cost of more than $1100 per study.

Staff Time Per Study

Perhaps the most interesting aspect revealed in our survey -- one that elicited the most actionable response from research sites -- relates to evaluating the time spent on various tasks performed by staff members during a study. Our survey asked very specific questions of all respondents in order to understand how much time they spend in each of 26 different tasks in three categories throughout the lifetime of a trial.

Clerical

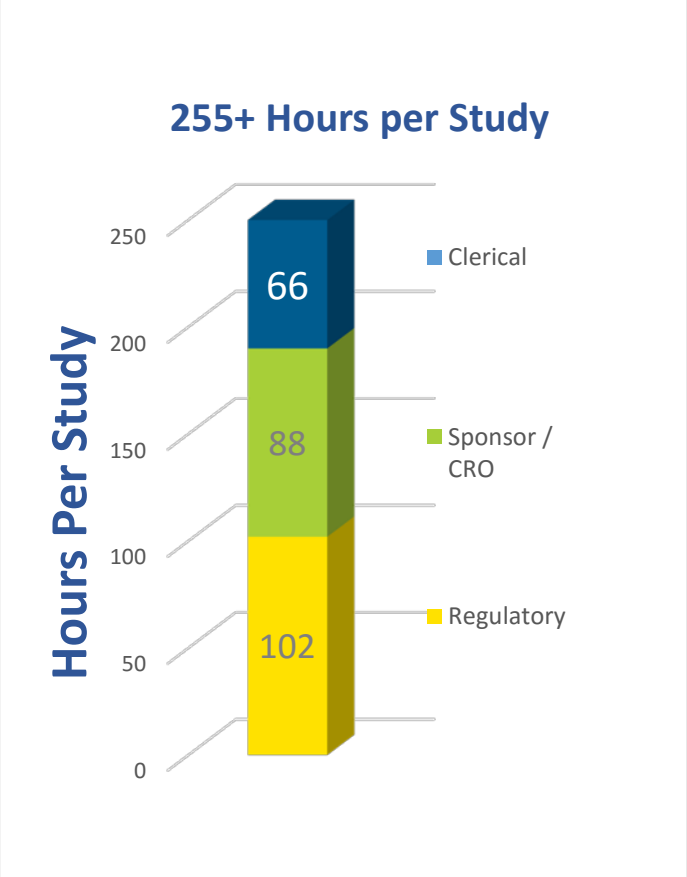
- Regulatory file preparation and creation
- Filing credentials and CVs
- Obtaining signatures

Sponsor/CRO

- Preparing for monitor visit
- Coordinating the monitor visit
- Monitor visit follow-up

Regulatory

- Review correspondence and documents
- Protocol-specific training
- GCP-related training



The tasks were bucketed into the three categories shown above. The Clerical category includes printing, filing, and scanning documents, and obtaining signatures from physicians. The Sponsor/CRO category includes tasks related to preparation and coordination of monitor visits, and the follow-up activities between visits. The Regulatory category includes tasks related to reviewing correspondence, documents and amendments along with the completion of GCP and protocol-specific training.

Overall, our survey revealed these tasks consumed an average of 255 hours per study. The survey data also indicated that over half of that time is spent on activities unrelated to regulatory matters. Instead, that time is focused on clerical tasks and other tasks associated with providing the information to the sponsor or CRO to review.

Clearly, there are opportunities for improvement. The question is, how can these opportunities be exploited? Should the time spent on these activities be optimized? Or can some of these activities -- such as creating and filing paper-based regulatory binders -- be eliminated?

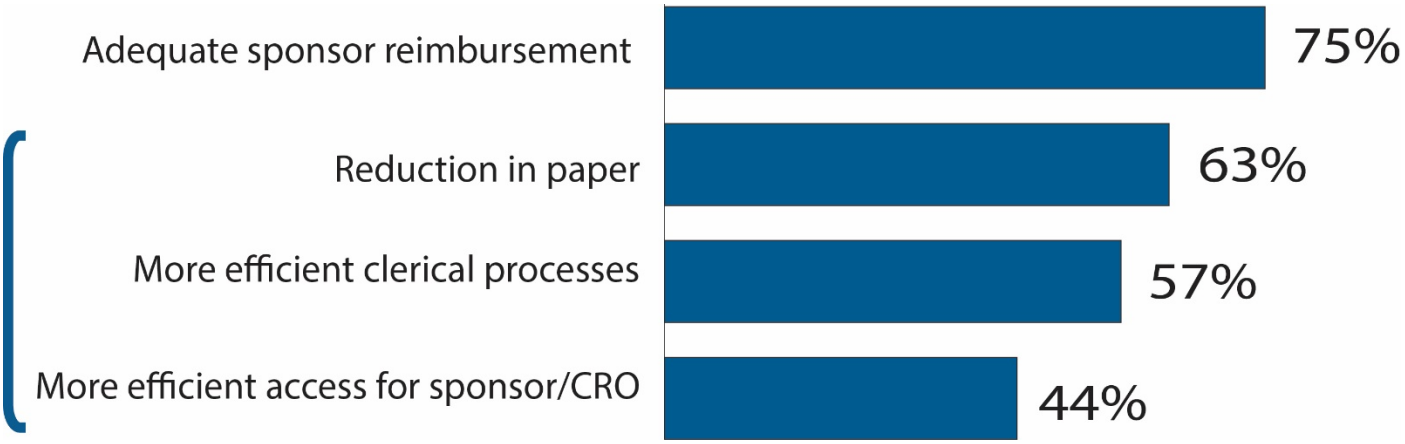
Cost Savings Per Study

Cost associated with regulatory task	% reduction	Est. Cost Savings Per Single Clinical Study
Staff time costs: $ 12,775	40%	$ 5,110
Material costs: $ 1,126	100%	$ 1,126
Total Cost Savings Per Study		$ 6,236

Preliminary case study data from Complion clients indicated that the transition to a more streamlined, electronic process for managing regulatory information produced an average 40% reduction in staff time costs, the result of a 100-hour reduction in the 255+ hours per study. That translates into an average savings of $5110 in staff time costs, and an average material cost savings of $1126, for a total cost savings per study of $6236, assuming CenterWatch's estimate of about $50 per hour for a regulatory specialist.

Opportunities for Improvement

Our survey asked respondents to identify the areas thought to be the most in need of improvement. As one might expect, the most commonly identified area was sponsor reimbursement. Obviously, if you are inadequately reimbursed for your costs, your operation is in jeopardy. But while increased efficiency can reduce costs, the matter of adequate sponsor reimbursement is ultimately determined by the specifics of your business arrangements with your sponsors.



So let's focus on those areas that can have tangible results in driving efficiency improvements. Topping that list is a reduction in the use of paper and the elimination of the need to manage and store paper documents.

Next on the list is increasing the efficiency of clerical processes. As described elsewhere in this article, clerical processes consume a sizable chunk of time, up to 60 to 70 hours per trial.

The third item on the list is improving access to regulatory information for sponsors, CROs, and other stakeholders.

Let's dig a little deeper into strategies for achieving these improvements.

> Getting rid of paper versions of regulatory materials would make a huge difference on efficiency and cost….regulatory binders are useless.

The statement above is another comment taken directly from our survey.

Obviously regulatory binders serve a purpose. Regulatory files must be available for audit, and the sponsor or CRO must be assured that those records are maintained in compliance with FDA and GCP requirements. But the binder itself is useless as an operational tool, of little utility as a workflow solution that can help you keep track of documents. It is nothing more than a record that you need to keep.

Opportunity #1: Save Time and Reduce Hassle

- **No Scanning**
  - Email Integration, Drag 'n Drop, and eForms
- **eSignatures**
  - Simple, Mobile PI-Interface and Coordinator Tracking

- **Digital Archive**
    - Secure, Cost-Effective Retention in PDF/A Format
- **Audit Readiness**
    - Binder Interface and Automatic Audit Trails

Getting rid of paper is really about saving time and reducing hassle. But how does one achieve a paper-less environment? Consider the potential impact if you could bypass printing and scanning documents. Instead, consider the following: What if documents received via email automatically entered a system where they could be managed digitally? What if electronic files could be entered into that system through a simple drag-and-drop process? What if you could create new files through an eForm? If there is no reason to print or scan information, how much time and money will you save?

Similarly, eSignatures, the ability to sign digital documents, can dramatically reduce the time and effort associated with chasing down physicians in order to obtain signatures.

Establishing a secure digital archive also reduces time and hassle by providing the means to store and manage files throughout the long-term archiving requirement, without the need for printing. Best practices associated with digital archiving can be implemented to insure a secure system in which records are not lost, deleted, or modified.

In addition, a properly managed digital archive means that you are always audit-ready. There is no need to expend the time and effort to physically prepare the right folders and materials.

Opportunity #2: Streamline Clerical Tasks

- **Standardize Process**
    - One Standard Nomenclature: Folders, Files, and eForms
- **Minimize Redundancies**
    - One Source of Truth: Staff Qualifications, Labs, and FWAs
- **Workflows**
    - INDSR, Staff Changes, QA, Start-up and Review / eSignature
- **Integration**
    - Streamline the Flow of Information Between Systems

The second opportunity for improvement focuses on streamlining clerical tasks. It’s worth noting that this process can have a significant pay-off even if you’re not moving into an electronic regulatory process.

The first step is to standardize your process. Implementing a standard nomenclature -- a standard set of tabs or binders, or a process for your regulatory team members or other individuals that are involved -- can save a lot of time and help to maintain audit-ready status. There is enormous value to be gained by knowing exactly where a document is going, and by keeping that consistent from one trial to another, or from one coordinator to another.

Minimizing redundancies is also essential. Often with paper files you may be storing the same document in many locations. For example, CVs or licenses might be stored in each trial. The same situation might also apply to labs or FWAs. A lot of time can be saved by creating a single source of truth and associating it with the appropriate resources, regardless of whether you are using an electronic system or creating notes in a file. Give careful consideration to how you structure and manage documents.

As part of your streamlining efforts, you should also create workflows for common tasks, including IND Safety Reports, startups, and staff changes, in order to properly manage associated documents. Workflows will also improve your ability to integrate and streamline the flow of information between CTMS, IRB, or other systems.

Opportunity #3: Collaborate

- **Regulatory Coordinators and Specialists**
    - Assign Tasks and Share Access Between Site
- **Secure Monitor Access**
    - Integrated Training for Read-Only Access
- **Investigators and Clinical Staff**
    - Notifications for Mobile eSignatures
    - Access Anywhere on Any Device

The third and final opportunity for improvement is all about collaboration, and your ability to reduce the time and effort expended on providing information to sponsors, CROs, other sites, and physicians. This is achieved by providing a secure solution that provides stakeholders with role-appropriate access to information. This level of collaboration can also help to ensure faster turnaround and AP [ph] compliance.

Takeaways

Our goal with the article was to provide an overview of the findings in the CenterWatch-Complion survey of research sites and medical centers. Those findings confirm the significant costs associated with the current hybrid paper system. But the findings also identify opportunities to reduce those costs and the time spent on clerical-, sponsor-, and CRO-related tasks. We hope this information will be useful in your efforts to reduce your regulatory burden.