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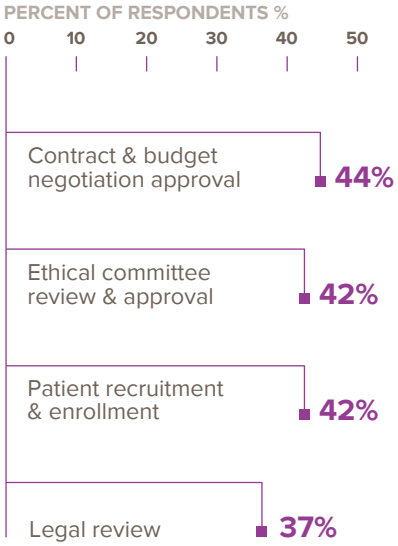
Faster Study Start-up

Clinical Document Exchange Details

CHART 1

Factors most often causing study delays (n=1,250)



Source: *CenterWatch Global Investigative Site Survey 2011*

Biopharmaceutical companies are facing intense financial pressures due to looming patent expirations, weak drug pipelines, and heightened competition. This tough scenario is driving them to explore strategies to improve operational efficiencies in clinical trials with a goal of speeding drugs or biologic treatments to market. One of the more inefficient steps in the clinical trial process — study start-up (SSU) — has been carefully scrutinized; and although efforts to shave hours, days, or weeks from clinical trial timelines have seen limited success,[1],[2] this step remains a bottleneck.

This white paper makes the case for use of an online portal for clinical trials, a technology that has moved beyond the introductory stages, but remains early in the adoption cycle for the life sciences industry. Currently, it offers great promise for improving document management and exchange as well as communication among stakeholders. Streamlining these functions will bring greater efficiency to the SSU process for sponsors, contract research organizations (CROs), and investigative sites by helping them adhere to increasingly more rigid clinical trial timelines.

Topics covered in this whitepaper:

- **Current status:** Document exchange during study start-up
- **Defining the portal**
- **Expanding portal adoption**
- **Building momentum**

Current status: Document exchange during study start-up

On an industry-wide basis, clinical trials often fall behind their timelines from the get-go. During the multi-step process of study start up, sites must be assessed, selected and activated; contracts and budgets negotiated; patient recruitment and enrollment strategies hammered out; and legal reviews and approvals by ethics committees completed. Each of these procedures can cause delay, and together, they have a compounding effect. A recent survey of clinical trial professionals highlighted delays in the SSU process, with contract and budget negotiations leading the pack as the top cause, followed closely by other SSU activities (Chart 1).[3]

1 *Stein, R. Project Zero Delay Accelerates Drug's Path To Clinical Trial, Medical News Today, August 4, 2009, http://www.medicalnewstoday.com/articles/159762.php, accessed May 5, 2012*

2 *Goldfarb MN. Standardizing CTAs: International Efforts. Applied Clinical Trials, 2005;14:48–53.Available at: http://www.appliedclinicaltrialsonline.com/appliedclinicaltrials/article/articleDetail.jsp?id=145641. Accessed June 12, 2012.*

3 *CenterWatch Global Investigative Site Survey, 2011.*

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CHART 2

Examples of study start-up documents

- Site feasibility survey forms
- Protocols
- Investigator's brochures
- Site contracts
- Budget work sheets
- Patient recruitment plans
- Informed consent forms
- Letters related to the study
- Regulatory documents to be sent to ethics committees
- Documents for shipping of study drug to the investigative sites

All of these tasks require document exchange among stakeholders, and inefficient document turnaround is often standard practice. This is due to the high volume of content sharing that must occur between sponsors, CROs, investigative sites, and external partners involving site feasibility survey forms, protocols, Investigator's Brochures, site contracts, and more as listed in Chart 2. Each of these documents needs to be reviewed, negotiated, revised, signed, managed throughout its lifecycle, and eventually archived.

What is the status of online document exchange?

It's fairly modest according to a recent survey, indicating a continued heavy reliance on unsecured and paper-based methods.

The survey, conducted in May 2012 by CenterWatch and Intralinks, a provider of online collaboration solutions including document exchange, gathered findings from 600 investigative sites across the globe.[4] Respondents were largely from North America (71% of respondents), but also from Europe (19%) and Asia (5%). They identified mostly as clinical research coordinators (58%) and investigators (23%).

TABLE 1: Online tool usage

TECHNOLOGY	2011 (n=389)	2012 (n=444)
CLINILCAL PORTAL	71 %	83 %
ELECTRONIC DATA CAPTURE	78 %	85 %

Source: 2012 CenterWatch/Intralinks Global Investigator Site Survey

The study revealed that 77% of respondents continue to use unsecured and often manual methods for document exchange (Table 1). A mere 20% claim to be sending documents mainly using an online tool. So, with more than three-quarters of respondents relying on inefficient methods that lack audit trails or version control, there is likely to be significant time wasted on tasks such as searching for documents, tracking due dates, and ensuring receipt of the correct version of the documents by the correct individual. Specifically, the study documented the following operational inefficiencies:

- 78% of sites reported re-sending documents to sponsors and CROs at least once or twice a week, and in some cases, more than five times
- 66% of respondents spend at least two hours, and 8% report spending six or more hours per week searching for documents .
- 58% of respondents track due dates for information, current status or milestones manually, using tools such as paper calendars, white boards, or to-do lists

[4] *2012 Intralinks Global Investigator Site Survey: Results available at: http://www.Intralinks.com/news-events/press-releases/2012/06/18/Intralinks-2012-global-investigator-site-survey*

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CHART 3

Characteristics of an online portal

Centralized
A central, sponsor-neutral portal serves as a single entry point to documents for all studies using a single credential. The portal becomes the single place of record for the latest versions of study documents and can be used to rapidly disseminate those documents as well as study-related information.

User-friendly
For the end-users — site personnel — the online portal must be a user-friendly technology that can be easily embraced to facilitate the continuing transition from paper-based activities.

Secure
A secure online portal provides security at three levels: system security, user access security and document security. The system has stringent user ID and password controls, and different role-based levels of user access.

Cost-effective
Staff no longer has to spend time searching for SSU documents in their latest versions, rather they can devote more time to productive tasks such as recruitment and patient enrollment.

Although these results are similar to those from the same survey conducted one year earlier, there are several outcomes signaling a shift toward greater use of online tools. In just one year's time, 74% of respondents reported having used an online tool for document exchange as compared to 65% in 2011. Of those claiming to be using online tools, 83% of 2012 respondents cite the online portal versus 71% from the 2011 survey. This represents a 17% change in portal adoption in one year (Table 1).

Respondents also identify anticipated benefits of online portal use. Topping the list at 71% of responses: "It will reduce the amount of paper I use." Some other anticipated benefits are:

- Being able to get up-to-date information right away (66%)
- Keeping track of information more easily (60%)
- Spending less time searching for information (49%)
- Reducing time spent on study management (41%)

A 2009 study conducted by Quintiles and Intralinks[5] highlights how much portal acceptance has grown in the past few years. In this survey of 252 clinical trial professionals, less than 10% of respondents reported using an online portal as the primary means of clinical trial document exchange. This number jumped to 20% by 2012 (Table 2).

TABLE 2: Current primary methods of clinical document exchange

METHOD	E-MAIL	WEB-BASED	COURIER	FAX
PERCENTAGE	64 %	20 %	8 %	5 %

Source: 2011 CenterWatch/Intralinks Online Survey

Defining the portal

An online portal that fronts a secure electronic document repository in a 21 Code of Federal Regulations (CFR) Part 11 compliant manner[6] can streamline document exchange and enable more effective communication — two key functions that impact SSU. To enable these operational efficiencies, an online portal must be (Chart 3):

- Centralized
- User-friendly
- Cost-effective
- Secure

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[5] *Intralinks Poll: Document Management Inefficiencies Cost Clinical Trial Sites Time, Money. June 2, 2009. Available at: http://www.Intralinks.com/news-events/press-releases/2009/06/02/document-management-clinical-study. Accessed May 7, 2012.*

[6] *FDA 21 Code of Federal Regulations (CFR) Part 11 – Electronic Records; Electronic Signatures. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1. Accessed June 11, 2012.*

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Currently, there is much discussion as to how information going through a clinical portal will become part of the eTMF, and over the next several years, answering this question may be a driving force behind greater use of clinical portals.

These features work in tandem to optimize the exchange of documents that occur as a clinical trial begins and continue throughout the course of the study. Each stakeholder plays a specific role, allowing collaborative partners to benefit from the portal in different ways. For example, as the study begins, the sponsor may use the portal to initiate much of the content to the participating sites across the globe. This effort can continue as the study rolls out. At the site level, the investigator is able to send and receive contracts and budgets quickly, and work toward faster resolution of this time-consuming start-up task. Also, sites will have immediate access to the latest version of study documents, resulting in less time spent searching for and handling papers. Further, all parties can communicate in a secure fashion.

For the most part, document exchange and improved communication is where the online portal market currently exists. Portals are already working closely with electronic document management systems (eDMS) and in the future, the next wave may evolve toward integration with existing electronic solutions such as electronic data capture (EDC), clinical trial management systems (CTMS), and electronic patient reported outcomes (ePRO), resulting in more automated workflow and actionable intelligence for the clinical trials team. Going forward, as portals integrate these systems, sponsors and CROs will face substantial challenges in mapping the capabilities of their existing systems and may look to the portal to fill gaps in workflow.

Other anticipated portal functions include the capability for safety report distribution, and integration with the electronic trial master file (eTMF). Currently, there is much discussion as to how information going through a clinical portal will become part of the eTMF,[7],[8] and over the next several years, answering this question may be a driving force behind greater use of clinical portals.

Expanding portal adoption

Sites, sponsors, CROs, and external partners all play critical roles in getting studies up and running. With continuing challenges in meeting study timelines,[9] stakeholders are increasingly proactive in their efforts to streamline SSU, which includes taking steps to expand portal adoption. As the 2012 Global Investigator Site Survey revealed, there is growing use of online portals for document exchange, but to optimize its impact, adoption needs to become more widespread.

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[7] *Healthcare Company Expects Online Collaboration to Save Millions of Euros. Sanofi. 2011. Available at: http://www.microsoft.com/casestudies/Case_Study_Detail.aspx?CaseStudyID=4000010130. Accessed June 12, 2012.*

[8] *Lownie K. In Search of Paperless Clinical Trials. Infonomics. 2009. Available at: http://www.bioclinica.com/News-and-Events/in-the-news/in-search-of-paperless-clinical-trials/. Accessed June 12, 2012.*

[9] *Tufts Centers for the Study of Drug Development. 2010 Survey of 3,516 Global Sites.*

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Looking ahead, the portal could become even more valued if it were to become the source of study-related communications such as short SMS news feeds, and mobile content access.

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Transitioning to an online document exchange portal represents a new process for many study teams, and as with any attempt to introduce new technology, there is an adoption curve.[10] Users are typically comfortable with their current workflow, so endeavors to implement change are often met with resistance and annoyance, even if they yield greater operational efficiency. This same rocky technology adoption curve is to be expected with the online portal, so it may be more realistic to encourage its acceptance in small steps, rather than an "all at once" approach. For example, companies might start with small pilot programs that focus on just a few of the portal's capabilities, and expand from there, rather than trying to assume comprehensive programs meant overhaul all aspects of SSU inefficiency.

It is noteworthy that EDC was mostly adopted in a piecemeal manner, as were other clinical trial solutions, such as CTMS, interactive voice response systems (IVRS), and ePRO devices.[11],[12] Over time, each has become ingrained in the clinical trials process, yet this raises another challenge. Each one requires a separate logon and password, so the idea of adding another one to access an unfamiliar online portal may hamper adoption rates. The issue of multiple logons issignificant as according to the 2012 Global Investigator Site Survey, 1/3 of responders claim to have at least six to ten different logins and passwords to access web-based clinical trial systems, with 20% claiming to have more than ten.[4]

Importantly, if clinical trial functions are integrated into the portal, the number of logons will be reduced, and the flow of information facilitated. For instance, as part of its document exchange capability, a portal can offer secure e-mailing to sponsors or CROs along with content. It can also offer e-mail alerts and reminders about required tasks. If this frequently used tool were linked to the portal, which provides audit trails, time stamping, and greater security than traditional e-mail, this function could be viewed favorably and help accelerate portal acceptance. And at least one logon would be eliminated, making the portal more likely to become part of daily workflow.

Looking ahead, the portal could become even more valued if it were to become the source of study-related communications such as short message service (SMS) news feeds (text messages), and mobile content access. It could also provide study news and FAQs as well as study-related questions and answers.

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[10] *Bleicher P. An Imposing Change: Embracing Electronic Data Capture Means More Than Buying Software; Companies Must Revise Old Processes. Pharmaceutical Executive, June 2004. http://www.highbeam.com/doc/1P3-652704421.html, accessed May 7, 2012.*

[11] *Claypool W, Bleicher P, Seguine E, Schuelke A. Easy Does It. Next Generation Pharmaceutical. March 2006 Available at: http://www.ngpharma.com/article/Easy-Does-It/. Accessed June 11, 2012.*

[12] *Bleicher P. Winning at EDC Implementation. Bio-IT World. 2004. http://www.bio-itworld.com/archive/031704/insights_winnning.html. Accessed June 11, 2012.*

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For the investigative site, attempting to track the status of the multitude of study start-up documents in their latest versions for all ongoing studies is no small feat, and requires capabilities that an online portal can offer.

Site challenges

For the investigative site, attempting to track the status of the multitude of study start-up documents in their latest versions for all ongoing studies is no small feat, and requires capabilities that an online portal can offer. This is especially true as sites perform greater numbers of complex studies,[13] calling for a degree of planning, procedures, and documentation that extend beyond the functionality of whiteboards or Excel spreadsheets. In addition, once the study is launched, sites must maintain the documents in an Investigator Trial File (ITF), a compilation of all trial information, in accordance with Good Clinical Practice (GCP) guidelines.[14] Often, sites continue to print the ITF and keep the papers in large binders that are unsecured and may require lots of storage space.

The online portal functions as a repository of all of the study documents in their latest versions, essentially creating an electronic ITF (e-ITF). The sponsor can upload documents to the eITF through the portal, but regulatory issues remain as to who has possession of those documents, particularly since GCP guidelines cite the investigator as responsible for maintaining specific study-related records throughout the study and for a period of time after it concludes.

As with other clinical trial technologies, embracing the portal is expected to be a significant challenge for sites.[15] They tend to be overloaded with work from multiple sponsors, each with its own system for study start-up, communication, and ongoing clinical data collection. This reality often leaves sites reluctant to learn yet another technology tool even though adoption of an online portal solution would mean all of a site's study documents would reside in one central repository, and each staff member could quickly access them with a single password.

Adopting new technology also means creating new standard operating procedures (SOPs) at the site and a commitment to staff training, a task that cannot be overlooked.[16],[17] Many study coordinators at the site may rebuff efforts to engage in more training for an additional system, especially if they are already computer savvy and view this as a disruption to their efforts to stay current with their studies.

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[13] *Getz KA. Rising Protocol Complexity, Execution Burden Varies Widely by Phase and TA. Tufts Center for the Study of Drug Development. Impact Report. May/June 2010.*

[14] *Code of Federal Regulations Title 21 Subpart D –Responsibilities of Sponsors and Investigators. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.4. Accessed June 10, 2012.*

[15] *Shapiro M. Poll Finds Ironic Inefficiency. Applied Clinical Trials, March 2009. http://www.appliedclinicaltrialsonline.com/appliedclinicaltrials/article/articleDetail.jsp?id=586857, accessed May 7, 2012.*

[16] *Tyson G, Dietlin T. Realizing the Promise of Electronic Data Capture: A Practical Guide. Campbell Alliance; 2006. http://www.campbellalliance.com/articles/Realizing_the_Promise_of_Clinical_EDC_A_Practical_Guide.pdf, accessed May 7, 2012.*

[17] *Neuer A. Technology Training: The New Must-Have. eCliniqua, May 27, 2007. http://www.ecliniqua.com/full_newsletter.aspx?id=71246&LangType=1033&terms=Ann+Neuer, accessed May 7, 2012.*

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A 29 month study of 75 sites performed by a provider of web portal solutions showed that by driving document management through a web portal, nine of the 22 weeks it takes to get to First Patient-First Visit (FPFV) could be eliminated, with a potential savings of $2.1 million.

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Fortunately, training to use an online portal can be minimal in comparison to learning expansive systems such as EDC or CTMS. Typically, training entails presentations at investigator meetings, online on-demand learning, access to a Help Desk, or use of DVDs. Training should take an hour or less, and should not be difficult for site personnel who are proficient Internet-users. Sponsors must support this effort and plan for training throughout the entire study, not just at the beginning. New hires, delays in recruitment, or onboarding of rescue sites are all occasions that require training mid-study.

Sponsor and CRO challenges

In deciding whether to implement a web portal to centralize document management and exchange among study participants, sponsors and CROs face numerous issues including: the need to generate new SOPs and establish new processes; concerns about the ability of the new system to integrate with the sponsor's or CRO's own portal; and costs of the initial investment and return on investment (ROI). This is a tall order for companies struggling to sustain pipelines in a challenging economic and regulatory climate. It is this environment, however, in which forward thinkers can affect the most positive change. They attempt to move their organizations away from the less-than-optimal status quo, and toward the implementation of best practices to position them ahead of the curve. In the case of clinical trial technology, making this move requires several factors — buy-in from upper management, early adopters to champion the technology within the organization,[18] and commitments to process change and ongoing training for existing and new staff.

Once a sponsor decides to move ahead with an online portal and plan for widespread adoption, there will be a learning curve and costs associated with changing SOPs and the internal processes needed to optimize the new technology's value. It is noteworthy that efficiencies linked to new technologies tend to be cumulative over time as end users become increasingly familiar with them through continued use across multiple studies.

Also important is factoring in opportunity costs, such as those tied to burdening staff with maintaining a paper-based system or a less-than-optimal computer-based process for handling, retrieving and storing SSU documents. As part of the evaluation, sponsors considering maintaining their own internally built portal must consider the costs incurred by continuing investments in software upgrades, expanding collaboration capability among internal and external stakeholders,

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[18] *Gladwell M. The Tipping Point: How Little Things Can Make a Big Difference. Little, Brown and Company, Boston, 2002.*

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A neutral online portal is key to improving document distribution, review and completion during SSU as well as facilitating communication among all stakeholders.

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implementation of standards, validation methods, security, and global regulatory compliance. Many sponsors lack the resources to support this massive effort internally, so their needs might be better served by transitioning to an online portal solution offered by a third-party provider. This step removes the burden of maintenance, integration of standards and support from the sponsor and CRO.

In building a business case for expanding web portal use for clinical trial document management and exchange, it is essential to weigh the financial investment of acquiring the technology and the potential time and cost savings it will afford against the cost of continuing with inefficient paper-based practices. By driving document management through a web portal, sponsors and CROs can potentially cut weeks from study start-up and site activation, yielding significant time savings and direct savings in operational expenses. As evidence, a 29 month study of 75 sites performed by a provider of web portal solutions showed that by driving document management through a web portal, nine of the 22 weeks it takes to get to First Patient-First Visit (FPFV) could be eliminated, with a potential savings of $2.1 million.[19]

Further evidence of potential time and cost savings can be seen in four case studies conducted by Quintiles.[20] The case studies tracked efficiency gains in SSU as the company switched from a paper-based process to a centralized online portal system. All studies used US-based sites.

Results from one of the case studies — Study A, a US-based study, which enrolled 50 centers and used one central institutional review board (IRB) — highlighted the value of a centralized portal for document exchange. The two hours per site that Quintiles staff would spend on activities such as assembling documents and instructions, completing shipping labels for the site, and verifying receipt of documents, could be done in ten minutes per site using the portal. This represents a 92% efficiency gain. In addition, by switching to the centralized portal, $9,000 in courier costs were eliminated over a six-month period.

As further validation of the portal's value, Quintiles collected metrics on the four studies in which the online communication tool was used for SSU activities (Table 3). There were substantial efficiency gains as compared to the CRO's traditional methods, which took an average of 120 days for academic medical centers (AMCs) using local IRBs, and 30 days for private sites using a central IRB.

Building momentum

At a time when the clinical trials industry continues its transition away from paper-based trials and toward greater adoption of web-based technologies, users are embracing these tools designed to streamline various pieces of the clinical development process. Much of the focus has been on compressing timelines once the trial is underway, but now the focus is shifting to making incremental gains in the study start-up process.

[19] *Shurell A. The Journey Toward Paperless Clinical Trials. Intralinks Webinar. 2009. http://www.slideshare.net/Intralinks/the-journey-toward-paperless-clinical-trials, accessed May 9, 2012.*

[20] *Ferrell L. Site Activation: How to Reduce Costs and Shorten Study Start-up Time. Quintiles/IntraLinks Webinar. October 2008. http://www.intralinks.com/transforming-business/webcasts/shorten-study-startup-time, accessed May 9, 2012.*

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TABLE 3: Efficiency gains with a web-based communication tool

STUDY	SITES	TRADITIONAL METHOD (DAYS)	WEB-BASED COMM (DAYS)	EFFICIENCY GAIN	TRADITIONAL METHOD (DAYS)	WEB-BASED COMM (DAYS)	EFFICIENCY GAIN
		PRIVATE	PRIVATE	PRIVATE	AMC*	AMC	AMC
A	60 Private	30	15	50%	—	—	—
B	14 Private 1 AMC	30	22	27%	120	97	19%
C	29 Private 21 AMC	30	20	33%	120	91	24%
D	50	30	15	30%	—	—	—

A neutral online portal is key to improving document distribution, review and completion during SSU as well as facilitating communication among all stakeholders. Using this approach, stakeholders are better positioned to keep studies on track, rather than allowing study timelines to veer off course.

Going forward, as consolidation and globalization continue in the pharmaceutical industry, greater collaboration will become necessary to bring more efficiencies to clinical trial operations. This effort will be facilitated via a portal, which can accelerate the site evaluation and feasibility assessment process, the drafting of budget worksheets, informed consent forms, and other documents related to SSU. Eventually, other gains may become available through the portal such as integration with ingrained clinical trial solutions and also electronic signatures, a complex issues with different regulatory guidelines worldwide.

Research indicates that only a modest amount of sites currently use a web portal as the primary method of communication for clinical studies, but the number has been growing steadily. Although there is a long way to go before the web portal is the default method of clinical trial communication, trends suggest this is likely to happen sooner rather than later as more functions become accessible through the portal. This ability of the portal to streamline SSU activities as well as other tasks involved in study conduct and close-out hold much promise for making measurable gains in the clinical trial process.