10 Things to Speed Development, Lower Costs, and Enhance Quality With Existing Clinical Budgets

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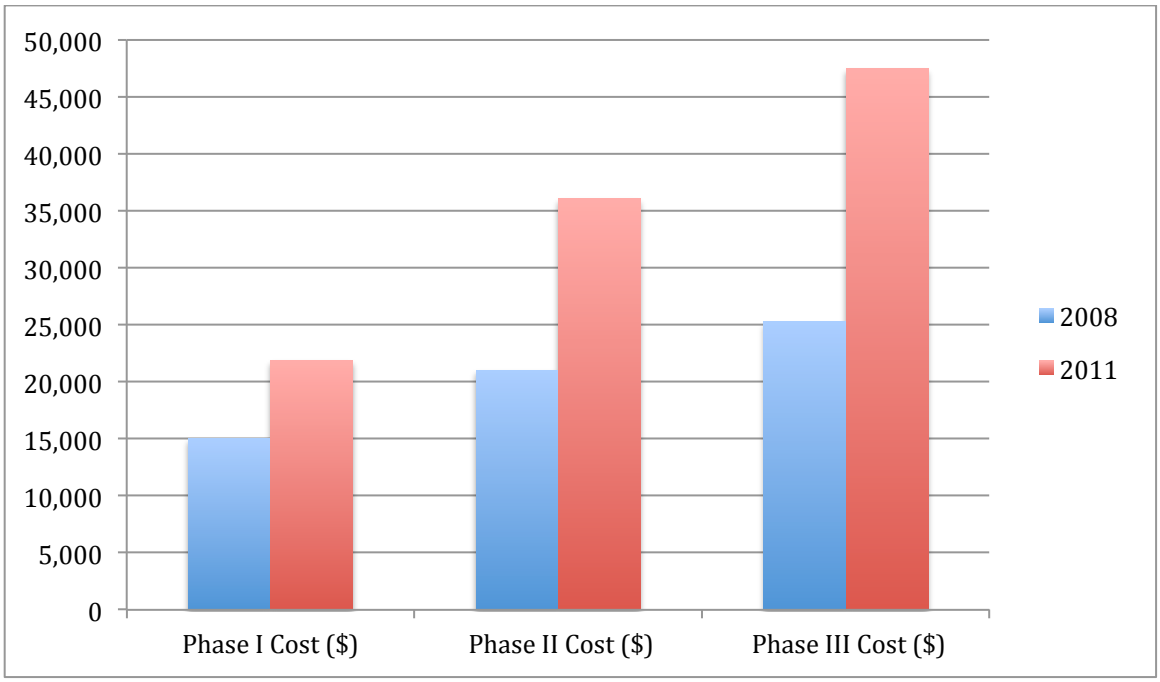
Small and midsized Pharmas, Biotechs, and Device manufacturers face many unique challenges. The most daunting challenge - the spiraling cost of clinical development.

Spiraling costs force companies to raise more money in a difficult economy or limit development to current budget constraints. Companies have few clinical staff and rely on contract research organizations (CROs) to do its clinical research. Spiraling costs will continue as Big Pharma, Biotech companies, and Device manufacturers shift more clinical development responsibilities to CROs in the future.

The cost to conduct clinical trials has increased for each Phase of trial between 2008 and 2011. Cutting Edge Informatics (CEI) surveyed 21 drug makers, 12 biotechs, nine device makers, and 23 CROs. Pharmalot reported CEI's results as shown in Figure 1. Phase I costs jumped from an average per patient cost of $15,023 in 2008 to $21,883 in 2011. In Phase II, the tab on a per patient basis jumped from $21,009 to $36,070, and in Phase IIIa, the per-patient bill rose from $25,280 to $47,523.[1]

Figure 1. Increase in Per Patient Costs ($) by Phase between 2008 and 2011[1]



This article contains concrete recommendations companies can incorporate now in its clinical development processes using existing budgets. Also included are development approaches and processes to help organizations eliminate waste and enhance cross-functional communication. These approaches work within and across development programs. These novel approaches empower Sponsors with new operational options for conducting trials. The result - more cost effective and efficient completion of critical clinical programs.

1. Standardize Data Collection Forms

Clinical research studies are regularly outsourced to multiple CROs during a development program. CROs develop case report forms based on the protocol. Small differences surface in the way questions are asked and in form annotations (discussed in #2 below). This makes the data difficult to combine. Additional cost and time is required to aggregate the data at the time of submission.

This minor decision causes further significant consequences. When data cannot be combined, reports spanning multiple studies must be hand-tabulated from tables or final study reports or by programmers hired to aggregate the data. This tedious task promotes error. It affects timelines and the resources needed to program data, review data, report to regulators, and to present data for licensing and partnership discussions.

Companies spend millions of dollars aggregating data for their submissions. With a little forethought, the time and costs for this effort can be eliminated or significantly decreased. Many companies do not plan to take its products to regulatory submission and question whether this approach provides added value. These companies derive value from this approach by saving time and development costs for Case Report Forms (CRFs) and study start up, aggregating data for due diligence, and ease of regulatory reporting.

The Food and Drug Administration (FDA) is moving toward requiring all data to be submitted electronically in a standardized format. In February 2012, the FDA released Draft guidance on providing standardized study data for regulatory submissions. The purpose is to promote the use of data standards in the electronic submission of study data to the FDA.[2]

About 80% of data collection forms contain common categories. Most Sponsors collect the following data for every clinical trial:

- Informed Consent
- Inclusion/Exclusion
- Demographics
- Vital Signs
- Medical (or surgical) History
- Laboratory Collections
- Adverse Events
- Concomitant Medications
- Randomization (not in all studies)
- Investigational Product Administration
- End of Study
- Comments

Combining data across different electronic systems usually becomes complicated because of simple differences in the name of the form, the SAS annotation, and the coding of the answers (is yes a 1 or a 0 in the back end codes). The changes introduced from one study to the next (a data manager's arbitrary decision) have nothing to do with the quality of the data or its use in data management for that trial. It has huge effects on the efficient use of the data within an entire development program.

Sponsors reap additional benefits when they specify the data collection format and maintain it across all data collected within a trial. Standardized forms must be developed for each study. These forms can be pulled from a Sponsor-specific library. Sponsor should include terms in every contract to ensure the exact forms shall be used and not developed *de novo* for each trial. The traditional time needed to design the case report forms for a trial is approximately 6-10 weeks and the costs for developing a CRF range from $20,000-60,000. Sponsors and CROs save significant time and costs using this method.

Trials may change over time and the edits for each trial may change. For instance, you may change the blood pressure range acceptable for enrollment in a study. Changes in edits do not change the underlying format of the data and the benefits of standard forms are still realized.

Data analysis for trials should be expanded to enhance the ability to identify fraud and protocol deviations across research subjects at a site. In 2009, Johnson & Johnson[3] and Icon[4] received a FDA Warning Letter for monitoring deficiencies in a trial they outsourced to Icon. In that trial, multiple patients reportedly received an injection at the exact same time at a single study site. These types of deviations were not picked up by the monitor, but would have been picked up by programmed analysis that evaluate data across subjects and not just within a subject's review. Cross-subject analysis of variance and data review is a critical component of trial oversight with Risk-Based Monitoring

Additional savings are realized if companies design forms for direct data entry. Rather than waiting for data to be transcribed, oversight of data can begin immediately, rather than waiting for data to be transcribed. An added benefite is better understanding of the errors made by an individual because the audit trail includes this additional information.

Clinical Data Interchange Standards Consortium (CDISC) leads the way in developing data and analysis standards for regulatory submissions. The FDA and many industry members participate in this process. In December 2010, the FDA's Center for Drug Evaluation and Research (CDER) released its Data Standards Plan Version 1.1.[5] It was not designed to be exhaustive, but to provide input to Sponsors from FDA reviewers to improve Sponsor's data submissions. The Center for Device and Radiologic Health (CDRH) and the Center for Biologics Evaluation and Review (CBER) are also working on standards. The CDISC Standard Data Tabulation Model (SDTM) provides the best format to use for data design. This forms the basis for the electronic submission format. The FDA now has a Study Data Standards Resources Web page to access existing standards. (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm.)

In January 2012, CDISC and the FDA presented an update on their efforts and what to anticipate in the upcoming months. They listed the top seven CDISC Standards Issues as shown in Table 1.[6]

Table 1. Top 7 CDISC Standard Issues

No.	Issue	Example
1	Waste of Space	Column Width "padded" beyond what is defined in the data set (e.g. cell length defined as 20 and 200 allowed for the cell size)
2	Extras	Adding extra domains not needed (e.g. supplemental domain for subject initials)
3	Validation Errors	Common errors include codelist mis-match, end date prior to start date, required and expected variables should be present in dataset, variable labels in the dataset should match CDISC naming convention, AE set to serious, but no qualifier has been set to "Y"
4	Extended Codelists	No example given
5	ISO Dates	Date issues can arise from invalid ISO 8601 partial dates. Start and end dates should contain similar length and character
6	Traceability	Creating SDTM from raw data is incorrect. Analysis Datasets should be created from SDTM
7	Inadequate Documentation	Supporting documentation should be in "Reviewer's Guide". Examples would include: Custom domains, what is in subquals, insufficient codelists, unfixable errors/warnings and why, derivation of key analysis variables

2. Standardize Annotation Across the Entire Development Program

In February 2012, the FDA stated, "clinical and nonclinical study data that were previously collected in a nonstandard format are not always easily amenable to complete standardization".[7]

As with standardizing the data collection (including the form name, the form questions, and the programming of the responses), standardizing both the SAS names and human readable labels make combining data significantly easier.

All similar data having the same SAS names and labels produces additional benefits. SAS programmers can program and validate data one time rather than for each study. This saves time and money. Standard programming across an entire development program gets top line results faster.

Planning to use SAS names in alignment for eCTD submissions (i.e., using CDISC SDTM standards) makes the downstream programming for submissions faster. It takes little or no more time to use these names across a development program. It costs no more if it is amortized across multiple studies.

3. Standardize the lab you use

Integrating laboratory (lab) data with clinical data is often a costly and time-consuming effort. It requires multiple interactions between data managers and the lab. Having a responsive, high quality lab with sound electronic systems and excellent quality control can significantly decrease the time needed for data lock. Sponsors often contract with labs without getting feedback from the data managers on the quality of the lab data exports. They may also forget to include costs for management of lab imports.

Integrating lab data into clinical data lowers monitoring costs and minimizes the risk of having clinically significant lab values missed. If lab values are integrated into the clinical data, then edit checks can highlight out of range lab values and assure the investigator assesses the lab value to determine any clinical significance. If the lab data are provided only on paper for investigator assessment or in a separate system, it is much easier to miss critical assessments of patient and product safety. When clinically significant lab values are incorporated in the clinical database, it assures adverse events are identified quickly without the need for a site visit.

Integrating lab data in the clinical data produces another benefit to the clinical development program. The safety of a medical product is key to approval. If each study is viewed in isolation and the lab data are only integrated at the time of regulatory submission for marketing approval, trends in laboratory values may be missed. For example, if there is an increase in creatinine for all subjects in one study, but values remain in the normal range, the risk of nephrotoxicity may not be appreciated until all the data across trials are combined. When the data are progressively integrated (based on the principles provided in this paper), then issues can be identified and addressed proactively rather than waiting until time for submission.

4. Eliminate silos: data and documents in one time only

A tenet of efficiency is to touch data once. Properly designed systems allow multiple users to access data and documents from many different links. When data or documents are only stored in one place, they cannot get out of synch and you will not have discrepancies.

Unfortunately, clinical research technology is developed and sold based on functional divisions within an organization (e.g., data management, regulatory, safety). Each group chooses a system to meet its individual needs. As a result, many different clinical systems do the same job. The same data and documents may be managed in multiple places and by multiple teams. Examples include the management of Serious Adverse Events (SAEs) and the management of Trial Documents such as the 1572, Financial Disclosure, and CV's. Duplicative activities add tremendous costs to clinical development programs.

Take trial documents as an example. Trial documents (both central and site documents) serve many different functions and are accessed by many different teams. For example, FDA form 1572 is used by the site to document the staff have the appropriate qualifications to conduct the study and the Principal Investigator (PI) has confirmed commitment to conduct the trial according to the protocol. This document resides in the site files and in the Sponsor Central Trial Files. In addition, the form is collected so the data can be incorporated into the final study report and submitted to the FDA. In a paper system, checking the accuracy and completeness essential documents for each Site may occur as many as 6-10 times (e.g. prior to sending clinical trial material, throughout the study by the monitor at the site, centrally to assure the central trial files are complete, at the end of the trial when the files are "locked", when completing the final study report, and during regulatory submission). Assuming 5 minutes per review of each document multiplied by 200 documents (conservative), savings exceeding $50,000 can be realized with this one simple change. Additional savings include costs of purchasing, maintaining, training, and reconciling across multiple systems and costs for monitors to travel to sites to review documents and assure the site and central files are aligned.

When Sponsors adopt technology to upload documents once, providing access by the appropriate staff (i.e., Sites, CRO, Quality Assurance, Regulatory) as needed, significant time can be saved across the entire organization.

Key electronic document system requirements should include: the rapid identification of missing documents, electronic signatures, role-based access, the ability to approve a document so it does not need to be checked multiple times, robust reporting capabilities, and the ability to have different archives based on function. For Companies wanting to out-license or partner its products, documents

are immediately available to facilitate a due diligence review. Access control can be used to make only the appropriate documents available for review.

Electronic document management provides several additional benefits. First, documents such as informed consent documents can be scanned or uploaded immediately for the monitor to review. Problems with informed consent are a key quality issue and reviewing informed consents immediately assures site performance issues are identified quickly and efficiently, minimizing the risk of harm to research subjects.

Some Sponsors have raised issues about online review of subjects' informed consent documents. It is acceptable (and responsible) to perform online remote consent review if the issues are addressed as follows:

- The informed consent document must explain the Sponsor's representatives will review trial documents, including the subject's informed consent document. This review may occur at the Research Site or electronically.
- The system used to scan or upload the informed consent forms must have adequate access control to allow only approved reviewers to see the subject's personal identifying information, which resides in the subject's signed informed consent document.
  An alternative approach uses an electronic system that enables role-based redaction of personal identifying information. This allows users, other than approved users, to see the documents with the exception of the personal identifying information.
- When electronic archives of the Site's Files are generated, they must be customized so the Sponsor's archive does not include the subject's personal identifying information. This can be accomplished by having the informed consents only archived for the Site archive and not in the Sponsor's archive. If a system with role-based redaction is used, then the Sponsor's archive will have the redacted version and the Site's archive would have the un-redacted version.
- An added protection can be added to the electronic informed consent review. The Sponsor should request the Coordinator scan the informed consent into the electronic system and certify the subject's informed consent is an exact copy of the subject's paper Informed Consent. The electronic informed consent form is then considered a certified electronic source. The Sponsor now benefits by having a document with an audit trail.

Electronic Trial Master Files (eTMF) eliminate the need to have a separate version of the files located physically at the site. If sites have direct access to their documents, they meet the requirement of having full control of the documents for their site with access at any time. When there is a duplicate version of the Site's Study Files, the time and cost for checking and reconciling two sets of files is considerably greater and the risk for error is much greater. At the end of the study, the site is provided with an archive of their site files, assuring complete documentation is available for site audits. This approach enhances quality oversight, minimizes onsite-monitoring time, and assures the site has all the key documents needed to confirm proper study conduct.

In larger organizations, process changes may be required. In every company, setting up these systems early, through contracts with service providers and through developing operating procedures for cross-functional cooperation and integration, provides significant long-term advantages.

In most organizations, the structure for study files (central and site-based) has been adapted from the DIA Trial Master File Reference Model. [8] This standard is used across all trials within an organization. Costs to adopt a standard system becomes less over time, lowering the cost per trial for the system in addition to the administrative savings previously discussed

Increased efficiency results when multiple functional groups, within and outside an organization, can access a common system. In selecting the best system to enhance cross-functional communications and eliminate duplicative work, it is critical to have robust systems for email notification as well as reporting capabilities. Many systems can also be used to provide notification of IND Safety Reports

and Periodic Safety Update Reports; saving significant time and cost for paper-based notification while providing audit trail documentation of delivering reports to investigators.

5. Eliminate Separate Safety Databases for Drugs in Development

Separate SAE databases are vestiges of paper data collection systems where SAEs had to be expeditiously reported before case report forms were returned to the Sponsor. Even today, most SAEs are manually entered into a system separate from the clinical database. The evaluation of the SAE continues and the opportunity for discrepancies between the databases also continues. Cost savings to reconcile the two databases may be significant.

With many electronic data capture systems, automatic notification of SAEs proceeds without the use of a separate safety system. The appropriate staff (across multiple functional groups and organizations) can be immediately notified by email and all work from a common database. This enables the team to update data in one place rather than in multiple databases. Automatic notification of adverse event data to US and foreign regulatory agencies can also be accomplished.

An accompanying document management system provides a storage facility for key clinical documents to support SAE reporting. These documents can be available to multiple functional groups (e.g., Clinical, Safety, Regulatory, and Medical Writing) and provide a better picture of the clinical profile of SAEs across an entire development program.

Coding can be done within the electronic system or the codes can be imported. By reviewing medical codes as development programs progress, identifying potential issues with certain adverse events can be accomplished earlier (e.g., identifying adverse events rated non-serious in some studies and as serious in others). No issues may be recognized if each study is reviewed in isolation, but potential issues may be identified when all data are reviewed.

Electronic data capture systems enable the analysis and reporting of SAEs across multiple trials. A clinical warehouse or specifically designed reporting tools accomplishes this goal. Capturing the AE's and SAEs for a development program allows prospective data analysis across an entire development program and across multiple indications for the same compound or device.

6. Modify the Monitoring Approach

Re-evaluating the way monitoring is accomplished in a trial yields significant cost savings and rapid identification of site performance issues. The Clinical Trials Transformation Initiative (CTTI) reviewed all FDA Warning Letters issued from December 1997- April 2009 for findings related to monitoring of clinical trials for CDER, CBER, and CDRH. There were 271 Warning Letters issued related to the monitoring of clinical trials. Many Warning Letters cited violations of more than one area and covered more than one research subject. There were 465 violations cited, with General Responsibilities of Investigator 21 CFR Part 812.1 (Devices) and Part 312.6 (Drugs and Biologics) representing 41% of the findings.

The most frequently cited violations identified during the Warning Letter review and the number of times each was cited are shown below (Table 2).[9]

Table 2. Findings from FDA Clinical Trial Site Audits for CDER, CBER, CDRH 1997-2009

Regulation	Regulation Classification	Number of Times Cited
812.100	General responsibilities of investigators (devices)	109
312.60	General responsibilities of investigators (drugs, biologics)	83
812.140(a)(3)	Investigator records of each subject's case history and exposure to the device	78
312.62(b)	Investigator recordkeeping and record retention: Case Histories	69
812.110(b)	Specific responsibilities of investigators: Compliance	65
812.140 (a)(2)	Investigator records of receipt, use, or disposition of a device	61

Using the gold standard monitoring plan of onsite visits every 6-8 weeks does not predict or guarantee the quality of monitoring. Using a CRO to conduct trials does not eliminate the Sponsor's responsibility for trial oversight. In 2009, Johnson and Johnson[3] and Icon [4] received 483's from the FDA for the same trial. In 2010, Pfizer received a 483 for monitoring deficiencies that occurred despite the monitoring plan showing 100% source document verification[10].

Quality is not the only issue. Djali recently reported monitoring costs as the highest single line item in their trials (Johnson & Johnson)[11]. It represented approximately 50% of trial budgets.

In July 2011, Ed Silverman wrote about a Cutting Edge Research report on Clinical Research Staffing. He reported, "Phase IV staffing increased by 85 percent from 2008 to 2011, while Phase IIIa doubled. Phase IIIb staffing rose 57 percent, Phase II staffing jumped 106 percent and Phase I staffing spiked 108 percent. One big reason – more clinical research associates. In 2008, the average Phase II trial employed 3.6 clinical research associates, but that rose to 9 in 2011. The average ratio of CRAs per site was 10 in Phase IIIb and 6.3 in Phase IIIa."[1]

Source document verification (SDV) is the most time consuming aspect of the monitoring process. In many cases, other key activities, including site education, are not completed due to the time required for source document verification. The FDA, EMA and ICH have all recommended more comprehensive remote oversight and less focus on onsite monitoring including SDV as the key quality measure.
It is the Sponsor's responsibility, regardless of who conducts the trial, to assure the study is conducted to the specifications of the protocol and the procedure manuals as well as to Good Clinical Practice. Electronic approaches provide the opportunity to use different methods to monitor, meet the goals of stringent oversight, and hold costs in check.

Strategies proven to provide better, higher quality, cost effective oversight are as follows:

a. Re-think Source Documents. How Sponsors use and review source documents for a trial significantly impacts monitoring costs. In general, 80-85% of the data collected for clinical

trials is collected specifically for the trial - it is not part of clinical practice. The trial data can be collected directly on forms designed for the trial, not extracted from medical records. These forms can be electronic source documents, source document worksheets, or case report forms. Monitoring of these electronic forms can be done remotely as soon as a subject has been seen in clinic, significantly decreasing the number and duration of onsite monitoring visits and enhancing subject safety.

When reviewing source documents remotely, monitors can spend more time on Site-specific issues, training, and meeting with investigators. Sites have reported they like the change in focus from Source Document Verification (SDV) and document review to more problem-oriented monitor visits.[12]

b. Review documents remotely, including informed consent. Collecting and reviewing documents remotely identifies problems faster, enhances trial quality and subject safety. Document review (particularly adverse events and informed consents) is a key performance and quality metric. When these documents are reviewed immediately, problem sites are more rapidly identified and remediation plans are implemented faster.

c. Coordinate cross functional review. The current system of data review is based on paper-based systems. When a Sponsor moves to electronic systems and eliminates the requirement for SDV before data review, the Site Monitor can review key data (source data review, SDR) and documents related to safety and inclusion criteria at the same time that the data manager is reviewing data on key assessments, IP dosing, and critical data without waiting for the monitor to visit the site. This approach ensures faster identification of safety issues.

d. Use Standard forms. Using annotated case report forms and edits across a development program can save costs for developing eCRFs and also for reports used for Risk-Based Monitoring.

e. Use a risk-based approach to monitoring. Focusing monitoring on high risk data and processes enables you to correct issues faster and to spend time and resources on the most important data. Adding a central oversight step that reviews data across subjects at a site and across sites provides a level of review that is not usually done until the end of a trial. Capturing site performance over time allows focus on the areas where a site needs additional helps as well as sites that are not performing to expectations.

7. Implement electronic investigational product (IP) management

IP management and control are key responsibilities for both Sponsors and Investigators. It is repeatedly listed as one of the top five FDA audit findings. Table 3 describes the results of the Top Clinical Investigator Findings from Clinical Trial Site Audits by the FDA Bioresearch Monitoring group in FY 2010.

Table 3. Bioresearch Monitoring Metrics for FY'2014: Top Clinical Investigator Findings [13]

Failure to follow investigational plan
Failure to maintain accurate Case Histories
Inadequate human subject protection—including informed consent issues
Inadequate accountability for investigational product
Failure to adequately obtain IRB approval

Table 4 describes the results of the TOP Monitoring Deficiencies from Sponsor and CRO audits by the FDA Bioresearch Monitoring group in FY 2010.

Table 4. Bioresearch Monitoring Metrics for FY'10: Top Monitoring Deficiencies[13]

Inadequate Monitoring
Failure to bring investigators into compliance
Inadequate accountability for investigational product

IP Oversight is a complex process. Data often reside in multiple systems, both paper and electronic. When the data on randomization, IP shipment and receiving, storage, administration, and destruction are provided electronically in a single report, monitors more efficiently identify and correct issues. In addition, onsite-monitoring time is shortened or eliminated because the majority of the oversight is done remotely.

8. Implement electronic monitoring reports

Electronic monitoring reports are more than paper forms in an electronic format. They include automatically generated reports from pre-existing databases for each of the following:

- Enrollment, Screen Failures, and Early Termination
- Safety including SAEs, clinically significant labs, and any deviation from the performance of the other sites in the study.
- Deviations
- Investigational Product Oversight
- Source Document Verification
- Informed Consent Review

The monitor saves significant time in generating the data and can spend more time analyzing the results of these reports - whether it involves training, meeting with the investigator, or helping the site put together a Corrective Action Plan.

From these monitoring reports, automatic notifications can be used to highlight Good Clinical Practice (GCP) issues. A report can be generated of all trial GCP issues and their status based on the data from these reports.

Free text is very difficult to analyze efficiently and should be kept it a minimum. Developing the forms to include choices for standard responses enables the data from the individual monitoring reports to support generation of metrics and site performance data across a study or business unit.

Adding sign off by the investigator can also save time in generating separate letters for each site post-visit.

9. Integrate Site Payment Programming Into Existing Electronic Systems

Managing budgets and site payments is a time consuming and error prone activity. The data in the electronic data capture system (or electronic source documents) and the documents provided by the Site determine Site Payments.

Linking the data from the EDC, electronic document system or Clinical Trial Management System to a payment module makes automatically calculated payments possible. This saves time and the error risk involved in manual calculation. The electronic audit trail and customization based on site contracts are added benefits of an electronic system.

When evaluating an electronic payment system, confirm you can generate payment reports made directly to the PI to assist in managing the reporting requirements of the Physician Payment Sunshine Act.

10. Develop Standard Performance and Quality Reports from Integrated Systems to Proactively Manage Trials and Identify Potential Quality and Operational Issues

In 2010, Djali et al [9] reported on a data-driven quality management system to manage compliance risk in clinical trials. This quality management system used an integrated data model to identify key sites that represented operational non-compliance and risk. The quality management system relied heavily on data from multiple sources (e.g., enrollment, number of adverse events, protocol deviations, deaths, monitoring report data, and essential document review) to develop risk-based scores for each site based on the deviation from the mean on each of the quality metrics.

Implementing this type of quality management system provides a more comprehensive view of site performance and combining it with the other recommendations described in this paper ensures a state of the art quality review method.

Conclusion

Sponsors pay for the design, development, testing, and implementation of these activities for every study. With efficient planning and proactive design, technology implemented for one trial can be used across multiple trials. By using this strategic technology approach, Sponsors benefit from spending less time in study start up, having better access to data and documents, lower study costs, and faster regulatory submission preparation.

The most successful companies will transition from manual and electronic systems used on a trial-by-trial basis to a comprehensive integrated technology. Companies can now use its current clinical trial budgets to achieve long-term savings and a competitive advantage in its development programs.

Systems designed and implemented to enhance efficiency, cross-functional communication, and data access bring true, measurable value to an organization.

References:

1. http://www.pharmalot.com/2011/07/clinical-trial-costs-for-each-patient-rose-rapidly/
2. Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Standardized Study Data February 2012. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf
3. Ball, M.D, Leslie K. "Johnson & Johnson Pharmaceutical Research & Development Warning Letter." Letter to Karen Grosser, Ph.D, M.B.A. 10 Aug. 2009. *FDA U.S. Food and Drug Administration*. U.S. Department of Health and Human Services. Web. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm177398.htm.
4. Ball, M.D., Leslie K. "Icon Clinical Research Warning Letter. 11/29/09. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm193156.htm
5. CDER Data Standards Plan Version 1.1, December 15, 2010. Office of Planning and Informatics. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm
6. CDISC Standards in the Regulatory Review Process 26 January 2012. http://www.cdisc.org/stuff/contentmgr/files/0/8d99d69f1195d2a2954e62d2fbb3470f/misc/cdisc_standards_in_fda_submissions_2012_01_26pdf.pdf

7. Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Standardized Study Data February 2012. Line 253-4. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf
8. Drug Information Association Special Interest Area Community for Trial Master Files. Version 1.2 released December 2011. http://www.diahome.org/en/homepage/EDM+Corner.htm
9. Clinical Trials Transformation Initiative; Effective and Efficient Monitoring as a Component of Quality: Final Report for Work stream 2: https://www.trialstransformation.org/projects/effective-and-efficient-monitoring/monitoring-project-workstream-2-define-key-objectives-of-monitoring
10. Ball, M.D, Leslie K. "Pfizer Warning Letter." Letter to Mr. Martin Mackay, Ph.D. 9 Apr. 2010.*FDA U.S. Food and Drug Administration*. U.S. Department of Health and Human Services. Web. <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm208976.htm>.
11. Djali, S, Janssens, S, Van Yper, S, Van Parijs, J, How a Data-Driven Quality Management System Can Manage Compliance Risk in Clinical Trials. Drug Information Journal 2010 44:359. http://dij.sagepub.com/content/44/4/359.
12. Radovich, C, Frick, J, Remote Source Document Verification (rSDV) A Sponsor Perspective and Results of Implementation. The Monitor, December 2009, p39-43.
13. BIMO Metrics FY 2014 http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/~~UCM~~443775.pdf

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MANA RBM is a focused on assisting the Pharmaceutical, Biotech, and Device industry in adopting the principles of Risk-Based Monitoring and Remote Trial Management.

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