As clinical trial IT expands in functionality, integration, and ease of use, considerable improvements to clinical development processes and timelines can't be far behind. Or can they? Today's market offers robust software for electronic data capture (EDC) and data mining, Internet-based portals for communication among clinical partners and regulators; and industry-accepted standards for data transmission and submission, yet a lack of adoption of these technologies has contributed to the median time between critical clinical trial milestones, actually increasing since 1997[1].

In 2004, Merck Capital Ventures (MCV), in conjunction with Science Applications International Corporation (SAIC), embarked on a study of key technology advancements and factors influencing adoption rates. The study identifies current challenges that stall IT acceptance and looks ahead five years to frame a picture of what the IT environment might look like as integrated broad-based electronic solutions are coupled with process change. Together, they are poised to realize more of IT's promised benefits, namely, improved cycle time and data quality, and greater cost effectiveness.

The research included interviews with individuals having direct experience in the clinical development process, particularly in IT and business process; discussions with experts within clinical development; reviews of proprietary industry-sponsored research; and extensive research of publicly available documentation.

What emerged is a picture of today's IT status from the perspective of seven core functions, ranging from protocol design to regulatory and safety issues (Figure 1). The study revealed, in part, a stubborn adherence to paper-based systems in the face of expansive, searchable, cost-effective solutions, but also a growing acceptance of IT powered by regulatory pressures to improve the efficiency of submissions and adverse event reporting.

To implement the requisite IT solutions successfully within the organization, the research cited process change as elemental. Without it, it is unlikely that new technology meant to improve core function operations will yield expected, significant long-term benefits[2,3]. In fact, some companies who are achieving short term benefits from new technologies without having changed existing processes now realize they have further entrenched suboptimal business practices, finding it even more difficult to make substantive changes.

Core Functions—
Targets for Improvement

- Protocol Design and Study Start Up
- Patient and Investigator Recruitment
- Clinical Trial Management
- Clinical Data Management
- Data Analysis
- Clinical Supplies
- Regulatory and Safety

Figure 1: Core Functions

Moving Toward the New IT State

It is widely acknowledged that the present state of clinical development remains largely a paper-driven process that is cumbersome, time consuming, and costly. Geographically dispersed stakeholders performing internal protocol review via paper copies delay study startup. Paper-based monitoring and reporting of adverse events slow response time. Response time and quality suffer, and data are not visible to the sponsor in real or near real time. Important metadata cannot be easily generated, and there is no simple way to search data to highlight problematic investigative sites or facilitate decision making early enough to make a difference. And whether trial data are stored electronically or with paper, they tend to be stored in disparate, incompatible systems and formats that complicate data entry, data exchange among stakeholders, query resolution, and data reconciliation during the trial and before database lock.

For many companies, however, change is underway. According to Thomson CenterWatch, in 2004, pharmaceutical sponsors used EDC and/or interactive voice response systems (IVRS) in 44 percent of Phases I - IV clinical trials[4]. This is a quadrupling of the percentage of trials using e-solutions as compared to just four years earlier. Contract research organizations (CROs) used EDC and/or IVRS in a similar volume of trials in 2004 (39 percent) and experienced similar growth in EDC and/or IVRS usage.

The increased use of EDC, however, does not belie the slow adoption of eSource data. Research suggests that eSource is very much in its infancy.

E-solutions success stories are emerging, however. Novartis, for example, reports having implemented EDC in 2001, and now uses EDC in approximately 60 percent of Phase I trials and nearly 100 percent of Phases II and III trials. As a result, the company claims to have reduced the number of contractors in the data management department from 90 to 20, and cut the number of queries to four per 1,000 data points as compared to 51 per thousand for paper-based trials. Cost has been slashed to $4.60 per page for EDC vs. $23 per page using paper. The median time for database lock dropped to four days with EDC vs. 10 weeks for paper. The company reports annual savings exceeding $100 million[5,6].

What is not known at Novartis, however, is the impact on costs along the entire clinical development process. Focused efforts, such as Novartis's EDC initiative and other impressive examples (Figure 2), demonstrate benefits but overall, victory remains uncertain.

Several sources report that clinical trial durations and costs have not been improving across the industry. Thomson CenterWatch and Pharmaceutical Research and Manufacturers of America (PhRMA) claim increased spending on clinical development[7]. In March 2004, the Food and Drug Administration (FDA) presented its current views on deteriorating drug development performance in *Challenge and Opportunity on the Critical Path to New Medical Products*[8]. Data presented in that report indicate that in the last five years, a 55 percent increase in investment is required to launch a new drug, and if biomedical science is to deliver results, there must be a focused effort on improving the medical product development process.

Best Practice Examples of Applying IT to Improve Clinical Trials Performance

- **Wyeth eClinical**
  Implemented an integrated electronic Case Report Form (eCRF) and clinical database and reduced errors and time from protocol design to database lock and final data analysis. Company reports having saved millions of dollars and reduced study duration from 38 months to 20 months.

  Source: *DIA 2004 Conference Materials*

- **NCI Informatics System**
  Implemented integrated databases, application integration and infrastructure technologies to support clinical trials. The agency reports time from first patient in to receipt of last trial data reduced by 75%, from 360 to 90 days. AE filing time reduced from 45 days to less than 10 days.

  Source: *Bio-IT World,* July 2003, Page 67

- **Eli Lilly Interactive Tadalafil Clinical Trial**
  Internet-based solutions used throughout this trial. Reduced time between last patient visit and database lock to 24 hours. Able to monitor more than 30 patient visits/day versus 15 patient visits/day via traditional clinical trials.

  Source: *DIA Journa*l 2004, Vol. 38, pp. 239-251

Figure 2: Best Practices

Understanding the Challenges and the Opportunities

The promise of IT to help streamline clinical development is perhaps best understood by defining its impact on the seven core functions of clinical development (Figure 1). Those functions figure prominently in the lengthy sequence of events beginning with IND submission and protocol approval, moving to patient enrollment, trial management, database lock, statistical analysis, report writing, and finally, regulatory submission. Each step along the way is fraught with challenges related to inadequate or an absence of technology, or the mixed use of electronic and paper-based methodologies.

One of the core functions, clinical data management, for example, involves collecting information from numerous sources such as investigative sites, CROs, and laboratories. Often, those data are collected in both electronic and

paper format, in the absence of collection standards, resulting in multiple trial-specific databases, an array of related systems, and extended time for data reconciliation. These systems, sometimes numbering into the hundreds within a single company[9], have become ingrained as legacy solutions and loom as huge barriers for change.

Another function, regulatory and safety, attempts the difficult task of integrating data from various functional areas throughout the trial process. Information from distinct databases/systems created for regulatory purposes tend not to be aggregated, limiting data mining capability and ability to respond to regulatory questions or investigate adverse events in a timely manner.

Core Function	Mainstream Process And Technology Characteristics In Three-To-Five Years
Protocol Design	▪ Wide use of study-specific protocol simulation and adaptive design ▪ Reduced number of amendments via improved decision support systems ▪ Collaboration tools used within project team and with investigator sites ▪ Improved workflow solutions with IRBs and Data Safety Monitoring Boards ▪ Expanded use of Web-based study start-up solutions ▪ Integration with label-driven design initiatives
Patient and Investigator Recruitment	▪ Earlier input and collaboration with investigator sites to help shape protocol for feasibility of enrollment, as well as assessing site's ability to meet the protocol ▪ Better access to site recruitment figures to alert for slow enrollment and to determine if help is needed to reduce time and cost of enrollment Wider use of site mining, assessment and screening tools ▪ Patient accrual, cost simulation and related monitoring tools ▪ Multi-pronged approach to patient accrual (site database, local advertising, and use of centralized recruiting databases)
Clinical Trial Management	▪ Near real-time visibility of project status across all studies whether in-sourced or outsourced, active or inactive ▪ Warning systems to identify problems or non-compliance early ▪ Better sponsor access to potential project team resources ▪ Continued outsourcing to CROs, using very defined performance metrics
Clinical Data Management	▪ eCRF, eCTD and CDISC standards are widely accepted leading to "bridge development" to/from legacy systems ▪ Leveraging existing EDC and electronic patient reported outcomes (ePRO), expanding eSource collection methods and improving active analysis of trial and clinical data to identify administrative, safety, or efficacy issues early
Data Analysis	▪ More near real time reporting and analysis occurring during trials (adaptive designs, patient adoption rates, site selection, etc.) ▪ Workflow tools used to streamline and document the process for easy repeatability and increased reuse of statistical programs
Clinical Supplies	▪ More use of integrated processes and systems for effective manufacturing, inventory, and distribution of small and large orders ▪ Continued use of IVRS and a growing use of Radio Frequency Identification (RFID) technologies to support better tracking and scheduling
Regulatory and Safety	▪ Faster and more effective participation via Improved cross-functional workflow management and database mining ▪ Use of database mining tools ▪ Shortened durations for document preparation and submissions through use of integrated databases/systems ▪ Global pharmacovigilance function that develops and implements risk management systems, including signal detection and signal management

Table 1: Adoption of e-Solutions Enables Movement Towards An Improved Process and Increased Business Value

The MCV/SAIC study suggests that the clinical development landscape may look quite different in three years (Table 1) as technology, business practices, regulatory, and competitive pressures align and integrate to allow e-solutions to address some of the existing challenges. As that happens, many of today's core functions will see real improvement.

It is worth emphasizing that business processes, comprised of workflows, tools, and resources, cannot remain stagnant for these technologies to make a difference. Couple this with regulatory mandates to adopt electronic solutions, and there is no doubt that momentum has started to re-defined industry practice. Figure 3 illustrates this alignment concept.

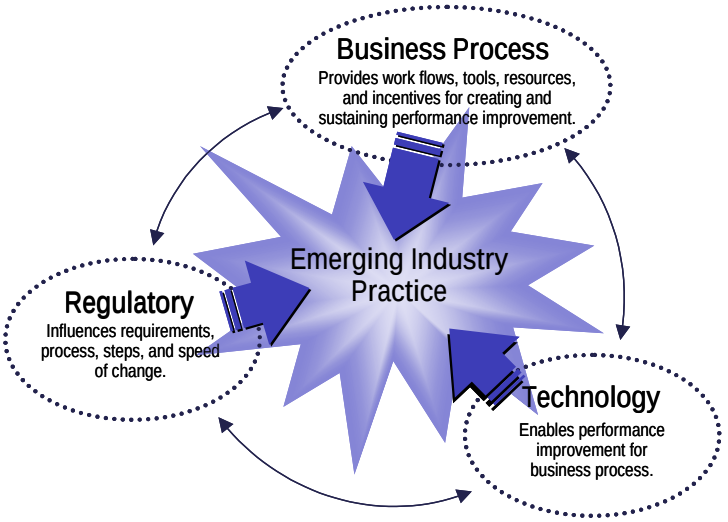

Figure 3: Regulatory, Technology, and Business Practice Alignment

Technology

Technology is the most tangible element of the improved clinical development environment. It is not elusive like business process or open to interpretation like regulatory guidelines. Technology is nuts and bolts—hardware, software, Internet, and intranet. Within its realm is an array of e-tools that enable the process overhaul that the industry needs. They offer greatly expanding functionality, allowing for integration of data and functions, as well as an infrastructure that will sustain improvements in communication and data exchange into the foreseeable future.

Table 2 illustrates the interdependencies within the clinical development process, and creates a basis for understanding technology's ability to affect the seven core functions. As the table shows, functional applications such as portals, collaboration, decision support tools and work flow management impact six of the seven core functions. Document management and project and portfolio management impact all seven.

It is not surprising that document management solutions affect all seven functions. It is a major challenge for pharmaceutical companies to handle the staggering amount of data generated throughout a trial contained in documents in multiple formats—paper, electronic, and digital—and sometimes requiring updating, or versioning, during the trial.

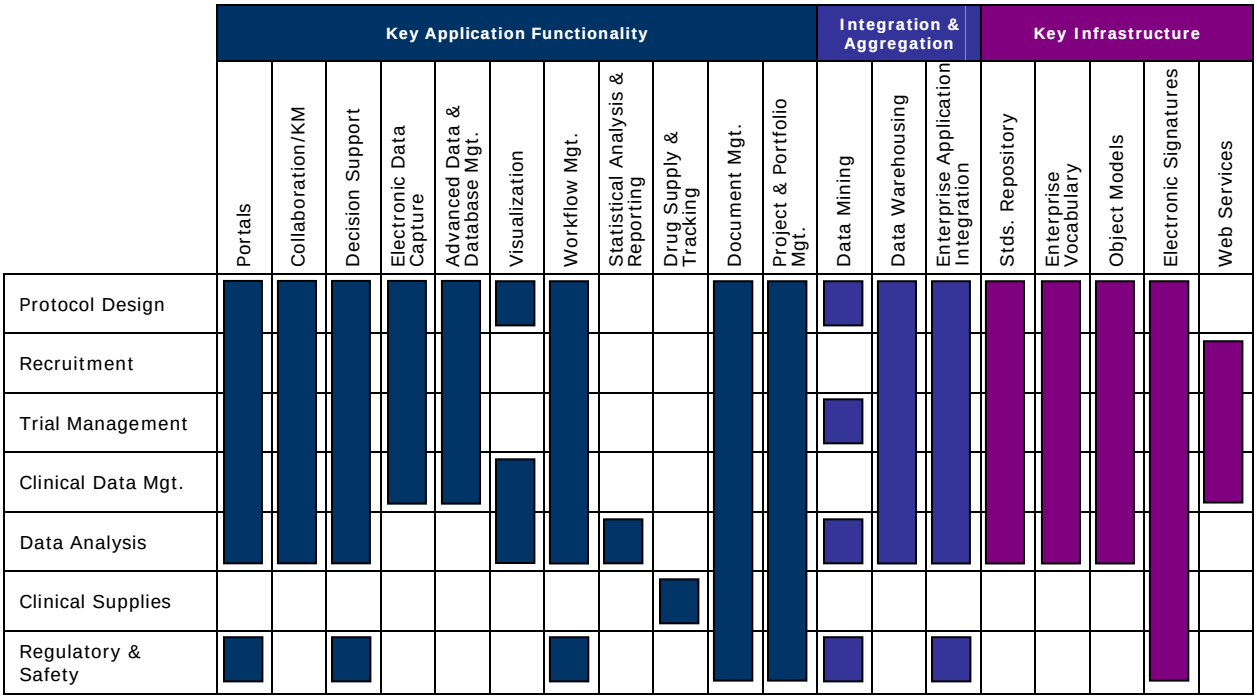

Table 2: Technology Map for Clinical Trials *Source: SAIC*

In addition to the volume challenge, document management becomes more complex as stakeholders begin to address the changing definition of a document. Two examples of new document formats are: Structured Product Labeling (SPL), a document markup standard approved by Health Level Seven (HL7) that describes the content of prescription drug labeling in an extensible markup language (XML) document; and the Electronic Common Technical Document (eCTD), an XML-based format defined by the International Conference on Harmonisation (ICH) that renders electronic regulatory submissions valid and enables content contained with the documents to be searchable and archivable by modules and sections, regardless of version.

Traditional document management applications are not designed to handle these new formats and their features. A robust document management system that provides a common repository with searchable attributes, electronic routing and approval, and life cycle management capabilities such as authoring, version control, and archiving are fundamental enabling technologies.

The Integration and Aggregation section of Table 2 refers to data mining, data warehousing, and enterprise application integration functions. Integration and aggregation of e-solutions allow sponsors to search and query data across all studies involving a specific product. Similarly, they allow regulatory agencies to search advanced databases and a broad range of data types to identify similar patterns in other drugs with the same chemical structure. This search capability, using visualization tools and adoption of centralized data, metadata, and vocabulary standards, is critical for early detection of potential safety issues and represents a major advance over non-searchable systems in which signals are possibly masked in data stored in multiple formats and locations and coded using different vocabularies.

Search capability, which Table 2 pegs as part of the integration and aggregation function, requires tools from the next component of clinical development—key infrastructure. Successful integration and aggregation involves development of a standards repository and object models to move the process forward. Standards adoption enables the following:

- Standards-based electronic case report forms (eCRFs/CRFs) that decrease time needed for database setup
- Reusable programs that generate standard tables, listings, and datasets, decreasing the time and programming resources required.
- Data being immediately available in the expected format for regulatory submissions (through the use of eCTDs)
- Cross-trial data may be pooled, facilitating data mining and the preparation of Integrated Safety Summary (ISS) and Integrated Summary of Effectiveness (ISE) reports

Business Processes

Implementing technologies that yield an expected high return on investment requires changes in business processes. These processes are the convergence of tools and resources and revised work practices. They are strongly influenced by regulatory guidelines that are creating specific requirements to which technologies and processes must conform (See Regulatory section).

The MCV/SAIC study suggests that over the next three years, forward thinking sponsors and CROs will increasingly respond regulatory and competitive pressures, by taking steps to improve processes that enable greater use of tools to automate data collection, management, and communication among stakeholders; increase adoption of data transmission and submission standards; increase transparency of clinical trial performance; and foster cross-trial efficiencies.

This won't be easy or cheap. Process change that is tantamount to system overhaul in the short term is hardly a realistic goal because of the enormity of the undertaking and the amount of change it would entail. People tend to resist these types of changes, as suggested by draft results of a 2004 CDISC survey in which 46% percent of sponsor respondents cited "concerns about changing current process" as a key reason for data collection technology adoption delays[10] (Figure 4). With each acceptance of a new technology, however, the enterprise nudges closer to its goal of system-wide solutions leading to greater operational efficiency and quality.

Acceptance starts with early adopters of technology promoting its value within the organization. Early adopters are believers or champions for the technology. They are risk takers. Theory suggests that there is a chasm between early adopters and the majority of users. According to a business text, *Crossing the Chasm*[11], early adopters seek change whereas the majority of users seek just the opposite—maintenance of the status quo. The majority are

Reasons Cited for Data Collection Adoption Delays

- Required Level of Investment (69%)
- Lack of perceived ROI (65%)
- Concerns with changing current processes (46%)
- Lack of Interoperability with Other Systems (43%)
- Resistance from investigator sites (40%)

Source: CDISC Draft Results of Research Project, 2004

Figure 4: Reasons Cited for EDC Adoption Delays

pragmatists who accept process change only when they have a compelling reason. Interestingly, the majority eventually becomes the biggest advocates for the technology when they start to believe in it. They spread the word, encouraging other pragmatists to accept it, too.[12]

This technology-acceptance model applies to any industry, but it certainly resonates with the pharmaceutical sector which has been notoriously slow to adopt electronic solutions despite evidence supporting the value of system-wide interoperable technologies. As the industry considers technology adoption, it is important that it not settle for a series of study-by-study or department-by-department solutions as this will, at best, yield minimal improvement, and at worse, add to the problem of legacy systems and create even greater costs in clinical development. Companies with cultures that recognize this are likely to reap the benefits of system-wide technology ahead of companies that lag behind.

The MCV/SAIC study also reviewed the practice of outsourcing the data management function. While it is too early to draw any conclusions, the initial findings highlight a few issues that are worth considering. For starters, to what extent does a stakeholder allow an outsourced partner to decide which technologies and processes to employ? Restricting them to existing ones limits the potential for benefits and can further entrench existing business practices. Allowing change will introduce risk but may also generate significant benefits. Many thought leaders are concluding that outsourced partners may be best suited for maintaining systems slated for retirement, saving internal resources for new development initiatives.

Regulatory

More than ever, the most significant factor driving the industry's deployment of IT in clinical trials is the adoption of data-related standards by regulatory agencies. FDA, for example, launched the Data Standards Council to coordinate the evaluation, development, maintenance, and adoption of health and regulatory data standards to ensure that common data standards are used throughout FDA and that standards are consistent with those used outside the agency.

FDA has provided guidance for submissions using the Study Data Tabulation Model developed by CDISC and has accepted CDISC's Operational Data Model for data interchange and archiving. According to FDA, the standards being developed by CDISC (Figure 5) are the centerpiece of the agency's vision for an IT infrastructure that can improve clinical development[13].

CDISC Standards

- Operational Data Modeling
- Submissions Data Standards
- Analysis Dataset
- Laboratory Standards
- Protocol Representation
- Exchange of Non-Clinical Data
- Case Report Tabulation Data

Source: http://www.cdisc.org

Figure 5: CDISC Standards

Additional examples of regulatory drivers include:

- Compliance with 21 Code of Federal Regulations (CFR) Part 11, the Electronic Records; Electronic Signatures final rule
- Global regulatory agencies mandating a proactive risk management approach for sponsors through initiatives, regulations, and guidance on harmonization of data exchange. For example, FDA receives adverse event reports according to ICH standard for information exchange, and ICH has issued E2B(M) guidelines that standardize the data elements for electronic transmission of Individual Case Safety Reports (ICSR).
- On May 1, 2004, European Medicines Agency (EMEA) started requiring suspected serious unexpected adverse reactions (SUSARs) be

reported electronically to EudraVigilance, the European data processing network

- On May 1, 2004, EMEA started requiring the registering of all trials into the European Clinical Trials Database (EUDRACT), requiring sponsors to submit data in an electronic format
- FDA plans to populate and mine clinical and efficacy data using the Janus data warehouse
- In December 2003, FDA issued a ruling requiring electronic submission of product labeling content, such as a pdf file, by June 2004, and a transition to the Structured Product Labeling document markup standard by July 2005
- The creation and adoption by ICH of the Electronic Common Technical Document (eCTD)

Further standards are expected to come from the Consolidated Health Informatics Group, an interagency organization in the U.S., and from the HL7 healthcare data standards accredited by the American National Standards Institute and accepted in many nations throughout the world.

The industry should also expect increased adoption of Electronic Health Records in U.S. and Europe and continued government and payer pressures for cost and cycle time reductions in drug development. Both will have an impact on the use of IT because both require efficient and effective data exchange and management.

Final Comments

The MCV/SAIC study identified three fundamental and interrelated forces driving change in the pharmaceutical industry: technology, business processes, and regulatory guidelines. Technological advances enable new workflows and promises of interoperability and integration of function, but technology alone has little power to create meaningful change. Successful implementation of electronic solutions requires changes in business processes and an appreciation of how difficult it is for organizations to take those first steps away from paper-based clinical systems that have worked for decades.

Ingrained behaviors are difficult to change, but with the help of internal champions, leading companies are managing to launch new approaches, perhaps incrementally at first, but eventually crossing the chasm to system-wide solutions. The results are indisputable: better quality data, accelerated cycle times, and greater cost efficiencies. Driving the move toward greater use of technology are regulatory forces that are focusing on improved collection, “searchability,” transmittal, and storage of data.

Figure 6 shows the push-pull of accelerating and limiting forces affecting technology acceptance.

Some companies will debate what an ideal solution could look like before making any move forward while others will wait, hoping to find the answer in a regulation or best practices document. In either case, the result will be unmet expectations and falling further behind. There are no ideal solutions, and reading about best practices and implementing them are very different. Companies that have set a vision for the future, support a culture for change, and implement processes and projects to move forward are generating tangible rewards, creating learning organizations, and positioning themselves to be industry leaders.

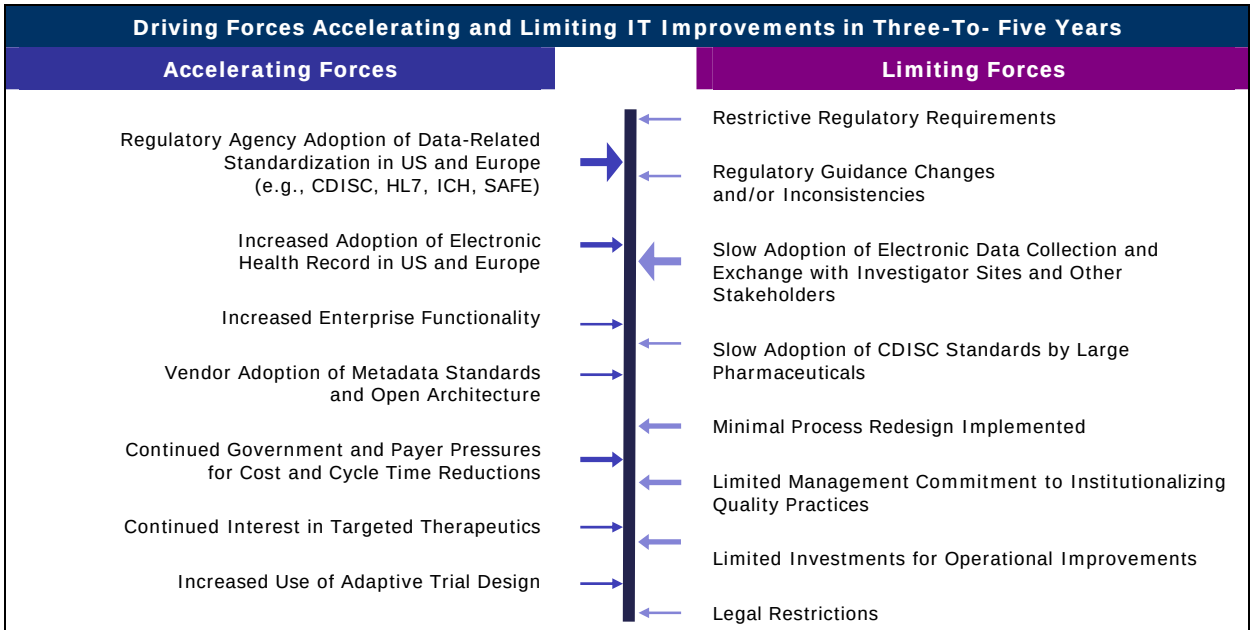

Figure 6: Driving Forces Accelerating and Limiting IT

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