The eClinical Forum[1]

and PhRMA EDC/eSource Taskforce

Present this Discussion Document on

The Future Vision of Electronic Health Records as eSource for Clinical Research

Version 1.0
September 14, 2006

[1] Formerly the Electronic Data Management Forum (EDM Forum)

General Information Document History

Document Name	**The Future Vision of Electronic Health Records as eSource for Clinical Research**		
Version	*Version Description*	*Date*	*Originator*
1.0	First Release	14-Sep-06	eClinical Forum / PhRMA EDC/eSource Taskforce Joint Team

Table of Contents

Table of Figures

1 EXECUTIVE SUMMARY

Healthcare Industry and Bio-pharmaceutical industry both strive for efficiency and quality while managing cost of patient data.

Both the Healthcare industry (physicians, hospitals, etc.) and the Bio-pharmaceutical industry (pharmaceutical, biological, and medical device industry) have the goal of improving patient health, but take different paths. Both paths have many similar needs, e.g. recording and managing information on patient experiences, and leveraging technology to manage efficiency, quality, safety and cost.

Today's transitional environment may at times seem like a step backwards.

The expansion and government-encouraged use of electronic medical record (EMR) systems in hospitals and physician offices means that patient data are increasingly being entered and maintained electronically. At the same time, clinical trial sponsor-supplied electronic data capture (EDC) systems are often used by healthcare professionals for entry of some of the same patient data as well as trial-specific data. Unfortunately, the data in most existing EMR systems cannot be used directly for clinical research purposes because of the variability of the data and systems and because the systems and infrastructures are not governed by clinical research regulations. Conversely, the sponsor-maintained EDC system is not appropriate as the only source for patient data as clinical research is not the main process flow for a healthcare practice, and research regulations prohibit the sponsor from having jurisdiction over the source data. In practice, this same information is often hand-written on patient charts prior to entry into the EMR and/or is printed to paper for hand-transcribing from the EMR into the EDC system. Sometimes, information first collected in the EDC needs to be backfilled to the EMR or patient chart in order to satisfy regulatory obligations. It is anticipated that this duplication of tasks and associated costs will grow with the increasing use of electronic data sources.

Planning must happen today for tomorrow's needs.

The ideal would be an environment where regulatory authorities can rely upon data from all electronic sources in carrying out their statutory duties and where data exchange between healthcare and research systems can occur in a manner compliant with both data protection and international research regulations. Such an environment would lead to efficient and robust methods of data collection and exchange, would ensure that both research and healthcare data are of high quality, and that regulatory approval of future therapies are based upon reliable and secure data sources.

The vision is for shared systems and processes that would allow the use of patient electronic medical data for clinical research in a way that meets data protection, regulatory, and ethical research requirements and thereby minimizes the challenges of clinical research for healthcare professionals.

In meeting this challenge, four areas need to be addressed:

1. A mechanism to utilize electronic medical information to support both routine treatment and outcomes for research purposes while satisfying regulatory and research requirements
2. Data standards such that the data can be consistently collected, interpreted and exchanged within the medical and research communities

3. Controlled, secure processes for releasing and transferring data from and to the EHR[2], device and research systems that are consistent with personal data privacy, clinical trial regulations, healthcare delivery regulations, and bioethical considerations
4. A process for allowing the bio-pharmaceutical industry to assist with funding and influence on national eHealth initiatives.

2 INTRODUCTION

2.1 Background and Rationale

The adoption of electronic medical records (EMRs) in both hospitals and private practice is on a steady incline. Recent reports suggest that 20-25% of US healthcare practices use electronic medical/health record systems (1), while within the hospital arena this figure is closer to 50% (34). Within Europe these figures vary greatly between countries and can be as high as 90% or more in the Scandinavian countries to under 20% in other countries. The growth is being driven by the need to manage healthcare cost drivers and to deliver more efficient and higher quality healthcare, while enhancing the safety of the patients. While there has been much media attention given to the national efforts of the US and the European Union (EU) to develop nationwide electronic health networks (eHealth), the following countries are in varying stages of planning and implementing systems and processes for capturing, maintaining and sharing electronic health records: Australia, Austria, Canada, Cyprus, Czech Republic, Denmark, France, Germany, Greece, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Norway, Poland, Slovenia, Spain, Sweden, United Kingdom, United States (3).

Alongside the growth in EMR/EHR, EDC systems are today used in an estimated 27-30% of clinical trials (4)[3], again in both hospitals and private practices. The use of electronic data capture technologies provides the opportunity to significantly enhance clinical trial conduct through improved efficiency and accuracy as well as the potential for real-time response to possible adverse situations. The data captured in clinical trial systems may be based upon a prior electronic source (eSource), such as EMR. Unfortunately, many of the EMR systems that manage the electronic source today cannot be used reliably for clinical research purposes because of the variability among these systems and the fact that they are not required to meet regulatory requirements for clinical trials. Therefore the data that are in the EMR system have to be printed or hand-transcribed and re-entered into the EDC system. The duplication of tasks, generation of paper and associated costs and inefficiencies, will only grow with the increasing use of electronic data sources. This could in turn put undue burden on offices performing both patient care and investigative clinical trials such that the quality of execution of associated tasks could be compromised.

The challenge is to develop a non-redundant environment where the bio-pharmaceutical and healthcare industries can benefit from data exchange in a manner compliant with both data protection and research regulations and where regulatory authorities can rely upon data from electronic sources in carrying out their statutory obligations. Such an environment would be efficient for all participants, and would provide quality research data based upon reliable and secure data sources.

[2] See glossary for distinction between electronic medical record (EMR) and electronic health record (EHR).
[3] This figure also includes electronic Patient Reported Outcomes (ePRO).

2.2 Purpose of this Document

This document is intended to 1) expand the discussion on the current EMR/EHR and EDC environments and 2) convince governmental (US, EU, etc.) and private groups involved in the planning and architecting of national eHealth initiatives that there is great value in involving the bio-pharmaceutical industry and that this value is consistent with the goals of national eHealth initiatives for improved patient care and accelerating the pace at which scientific discoveries in medicine are disseminated into medical practice. In particular, involving clinical trial professionals from this industry in the early planning can result in EHR data structures, infrastructure, and processes that are geared for long-term use in multiple industries. We hope to persuade designers of government-sponsored eHealth initiatives and providers of EHR systems (private market vendors), of the feasibility and practicality of the vision and to persuade them to include requirements for integration of clinical studies. We will identify the benefits that implementation of this vision can realize, as well as identify regulatory needs and potential next steps toward achieving this goal.

Several industry presentations and position papers have discussed the role of the bio-pharmaceutical industry in national eHealth initiatives. In particular

- the PhRMA IMPACC paper on the Role of the Bio-pharmaceutical Industry in the Growth and Adoption of Health Information Technology (HIT) in the US Healthcare System (27) seeks to inform industry leaders about HIT and persuade them to participate in the development and adoption of HIT, and
- the CDISC Electronic Source Data Interchange paper (19) reviews the regulatory requirements for paper and electronic source and explores the potential roles of the CDISC standards given several compliant eSource scenarios.

We offer this paper in addition, to present a future vision of how patient data, already collected by physicians and entered into electronic systems, might be leveraged for clinical research in conjunction with trial-specific data collected in the same efficient and regulatory-compliant manner thus benefiting healthcare professionals, patients, regulatory authorities and sponsors of clinical trials. The authors of this paper are experts in the area of electronic data capture of patient data used in clinical trials and can lend valuable insight into the future of clinical data capture, given the continued progress of national efforts toward individual electronic health records and the sharing of this data among healthcare providers.

2.3 About the eClinical Forum

The eClinical Forum (formerly the Electronic Data Management Forum) is a transatlantic, not-for-profit and non-commercial, technology independent group representing members of the pharmaceutical, biotechnology, and allied industries. The eClinical Forum mission is to serve these industries by focusing on those systems, processes and roles relevant to electronic capture, handling, and submission of clinical data. For further information: eClinical Forum, 68 rue de Rhinau, 67860 Friesenheim, FRANCE http://www.eclinicalforum.com.

2.4 About the PhRMA EDC/eSource Taskforce

The PhRMA (Pharmaceutical Research and Manufacturers of America) Clinical Trial Electronic Data Capture (EDC)/eSource Taskforce was initially chartered in August 2000 by the PhRMA/FDA Electronic Regulatory Submission Working Group to identify ways to advance the use of electronic clinical data capture. Sponsorship was transferred in 2003 to PhRMA's Biostatistics and Data Management Technical Group. The mission of the EDC/eSource Task Group is to facilitate the adoption of EDC for clinical trials and the inclusion of EDC data in regulatory submissions, with the intent of allowing clinical

investigators, bio-pharmaceutical sponsors, and regulators to fully realize the benefits of EDC and other related technologies. Membership includes industry representatives from Data Management, Clinical Informatics and Regulatory groups of PhRMA member companies, and liaisons from PhRMA's Bio-Research Monitoring Committee and Health Outcome Technical Group. This group has had meetings with FDA representatives from CDER, CBER, and the Division of Scientific Investigations (DSI) to discuss their work and ideas.

2.5 Authors

Authors of this paper are members of the eClinical Forum and PhRMA EDC/eSource Taskforce from the bio-pharmaceutical industry working in the areas of Clinical Data Capture and Management, and Clinical Informatics.

Michael Bartlett, Suzanne Bishop, Catherine Celingant, Gary Drucker, Tricia Gregory, Linda King, Susan Klimek, John Mestler, Brad Michel, Richard Perkins, Sharon Powell, Christian Reich, Selina Sibbald

2.6 Providing Feedback

If you have opinions or information that you feel would be of benefit to groups working with electronic clinical trials, please contact:

eClinical Forum
Email: info@eclinicalforum.com

3 CURRENT SITUATION AND TRENDS

In order to evaluate the feasibility and practicality of making changes to any environment it is important to first understand all areas of that environment. When conducting clinical trials, the environment includes healthcare providers and systems, the clinical researchers and systems, the source data, the regulations that govern clinical research and research data, and the standards that prescribe formatting for data content, data integration, and data exchange.

3.1 The Current Healthcare Environment

There is currently a global movement toward the transformation of healthcare through the use of information technology. Many countries have community or national initiatives underway. This is driven by projected improvements in patient safety, general healthcare delivery, and overall cost. Healthcare payers also have a vested interest in these initiatives since billing and payment efficiencies will be a by-product of an all-electronic healthcare record system.

In order to spur this movement toward a paperless healthcare environment, there are several barriers that need to be overcome, including psychological hesitations that exist toward changing from a paper to a paperless environment. In addition, the agreement on and introduction of data standards at the local, state, country, and international levels is needed to increase computer utilization and awareness in physician's offices and hospitals. In some areas, data standards have been approved, but cross-boundary agreements and implementation are still desired. There are concerns over the perceived disruption in the doctor-patient relationship imposed by computer use during their sessions, however, can be minimized through use of devices such as tablet PCs and PDAs. Still, there are concerns that current privacy regulations are not stringent enough to ensure patient data confidentiality in all cases, particularly in an electronic world. And of course, implementation cost of moving toward a paperless environment needs to

be justified.

3.1.1 Objectives of eHealth Initiatives

While there are many eHealth initiatives around the world with varying approaches, all share a common desire to:

a) Enhance patient safety
Medical errors may account for tens of thousands of preventable deaths in hospitals each year:
- The Committee on Quality Healthcare in America (5) estimates that medical errors could account for 44,000 – 98,000 deaths in the US alone.
- In the UK, the National Patient Safety Agency has been set up with the goal of improving the safety and quality of care through reporting, analysing and learning from adverse incidents and 'near misses' involving National Health Service (NHS) patients.

Many of the deaths and other incidents are thought to be the result of a lack of collated patient-specific information and/or accessibility of experience-based medical best practises. Medical staff cannot be expected to remember all aspects of every single potential problem that a person may present with – it is just not humanly possible. The ability to access all data pertinent to an individual person at any one time through a networked EHR allows the medical practitioner the most comprehensive view of their patient's condition and supports fully informed decision making. In addition, the use of electronic systems storing and presenting information about medications, available dose amounts and indications can substantially reduce prescribing errors caused by poor handwriting and similarities in names between certain drugs.

b) Improve quality of healthcare delivery
At no time in history has the growth in knowledge and technologies in medicine been so profound, yet healthcare delivery systems are floundering in their ability to provide consistently high-quality care (17).

A patient's healthcare is largely dependent on the collection of past and present health status information and the healthcare provider's ability to retain and retrieve learned medical information and updates. These form the basis for the healthcare provider's decision regarding a course of treatment. Paper-based collection of these data with its inherent legibility, accuracy and completeness issues provides a poor platform for making these healthcare decisions. Electronic healthcare can help improve the quality and completeness of the information by implementing rules that proactively identify potential errors and interdependencies and alert the healthcare provider. Based on this now more accurate information and experience-based treatment templates, intelligent healthcare decision support systems can go so far as to suggest a course of appropriate clinical treatment not otherwise considered by the healthcare provider.

Treatment assessments can be made much more broadly once patient health records reside in electronic databases. Organizations can use the electronic data to analyze treatment approaches across the patient spectrum rather than independently. Based on these analyses, viable treatment options can be presented to the healthcare provider to identify the best course of treatment for a patient.

Recently Pay for Performance (P4P) programs have been designed to reimburse healthcare providers for improving their healthcare quality and overall performance. US Federal government P4P initiatives have been discussed, developed and implemented in collaboration with private stakeholders with the intent to

assess whether these initiatives can lead to improved overall patient care and eliminate unnecessary healthcare costs (29). The American College of Physicians indicated that P4P reporting should be based on "valid and reliable clinical measures, data collection and analysis, and reporting mechanisms" and see HIT and EHR as supporting this need (30) In 2005 the American Geriatric Society and 70 other national medical societies recommended a five-year phase-in to P4P that in 2007 would include the beginning of "Pay for reporting" where physicians would be compensated for implementing information technology that support quality improvement (31). Another approach was recently reported where a study by Healthcore demonstrated savings to healthcare providers through use of payer-based health records (PBHR). The PBHR tool provided clinically relevant data that had been summarized and had "clinical intelligence" algorithms applied to it. Clearly EHR will play a significant role in P4P as a healthcare provider and payer data collection enabler.

c) Reduce healthcare costs.
Paper-based healthcare systems are expensive and unable to consistently deliver recommended patient care, particularly for chronic diseases, due to the fact that the information is scattered throughout numerous files/locations and not easily gathered or viewed as a whole. In the US alone it is estimated that investment in standardized electronic healthcare information exchange could deliver $77.8 billion in annual healthcare savings (6). This is mainly derived from reducing redundancies between different services, such as duplicate records with basic details for the same patient being maintained at multiple locations, and reducing the large amounts of resources and time taken to support and administer all these independent records. The EU has invested many hundreds of millions of Euros in preparing the framework for an interoperable network of EHR systems, and contracts have been awarded in many countries to begin implementation. The savings are expected to be substantially greater than the investment, with the clinical benefits of improved safety and quality outweighing the financial gains.

d) Develop Person-Centered Health systems
In an EHR system, information would move with an individual across healthcare facilities, regions and countries, providing comprehensive knowledge of any medical conditions and facilitating appropriate treatment regimens. This also could support providers identifying patients that fit tighter criteria and treatment specificity for entry into clinical studies.

3.1.2 Adoption of Electronic Health Records

Within the EU, the Action Plan for Health mandates that each member country will have an outline for interoperability of electronic health records in place by the end of 2006 (7). Many European countries are moving rapidly toward this goal with extensive restructuring, development of technology infrastructures and changes in procedures and policies. In the US, the Office for National Coordination for Health IT (ONCHIT) launched a range of activities during 2004/2005 which are designed to provide direct technical assistance toward the same goal.

Within both the US and Europe, it has taken longer than might have been expected to start this process, and not everyone has moved at the same pace. Consequently, as Figure 1 illustrates, even within Europe, where EU-wide agreements and socialized healthcare provide a framework for co-ordinated development and implementation, some countries are more advanced than others in the introduction of an electronic healthcare environment.

The US has seen a slower movement toward electronic health records, attributed to a healthcare environment based on multiple private-practice providers and reimbursement schemes (8). This has been further hampered by a fragmented EMR/EHR market, where multiple vendors are vying for their share. It is known that some larger healthcare institutions have tried more than one EMR system and that for some

a high level of customization has occurred, making sharing of information difficult, even within the same system installed at one institution. Indications from the most recent Medical Records Institute survey show that a lack of adequate funding and resources are still considered the most rate limiting factors (33). Even finding a suitable EMR/EHR system is difficult as a complete solution may involve multiple vendors and IT platforms. Other areas of concern include lack of support by medical staff, lack of migration plans from paper to electronic records and how to actually assess an EMR/EHR system to ensure it meets technical and operational requirements.

In emerging markets the adoption of EMR/EHR is still low. In remote areas, even where EMR is used at a basic level, sharing data between EMR/EHR systems remains an issue to be addressed

However, what is clear is that most countries are accelerating the transformation so that throughout Europe and the US, the intent is to have a high level of interoperable EHRs implemented during 2007 – 2014 (9).

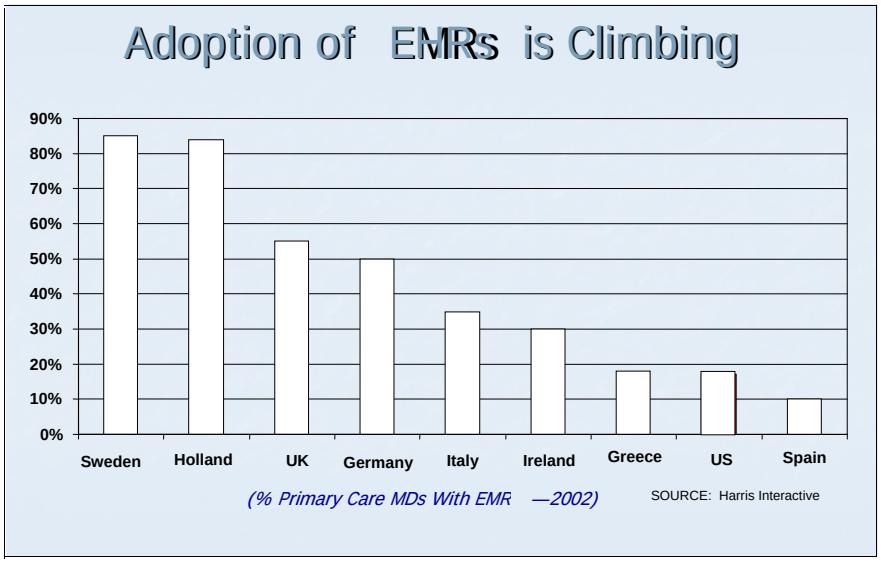


Figure 1: The Adoption of Electronic Medical Records Is Growing Globally[4]

As institutions move toward electronic patient records, the use of a computer during consultations becomes the norm. The formerly perceived barrier of the computer in the doctor-patient relationship is being eroded as practices change with a new generation of computer-aware physicians and patients. As a result, it has become not only possible, but in many institutions commonplace, for the physician to access and enter patient notes directly into the computer in front of the patient. This trend is also likely to have an impact on the comfort of physicians with the direct entry of patient data for clinical trials.

3.2 The Current Clinical Research Environment

[4] See glossary for difference between EMR and EHR. These figures are from 2002 and a more recent comparison is not available. However, a recent report (1) shows that the US figure was 20-25% in 2005, and one can expect that other countries have also increased in the past 4 years.

Bio-pharmaceutical companies typically conduct *prospective* clinical research, which is subject to regulatory oversight. Data collection for prospective clinical research is done via paper or electronic data capture (EDC). Academic and other researchers frequently conduct *retrospective* and epidemiologic clinical research, using data mined from EMR systems. The requirements for this type of research are far less stringent than those governing the work of researchers conducting prospective clinical trials to test the safety and efficacy of new drug candidates. For the purposes of this paper, the term "clinical research" will refer to prospective clinical research, which is subject to regulatory oversight.

The use of electronic data capture (EDC) by the bio-pharmaceutical industry to conduct prospective clinical trials on new drug candidates is growing as bio-pharmaceutical companies face increasing pressure to bring new, innovative products to market faster and in a more cost-conscious manner than ever before. At the same time, increasing concern over product safety has resulted in the need for more and longer trials, causing costs and time-to-market to increase. The use of EDC is seen as a way to improve data quality and drive efficiency in the clinical research process. However, the transition from paper to EDC has not been a smooth one, and the bio-pharmaceutical industry understands that EDC is not the whole answer.

3.2.1 Electronic Data Capture

EDC is a technique for collecting clinical trial data in such a way that they are delivered to the sponsor in electronic form instead of paper. This includes the following scenarios:

- Information that is first recorded on paper by the investigator's staff or the patient , is subsequently entered into a computer at the investigator's site, and is delivered electronically to the sponsor or sponsor's representative (such as a CRO) without a hand-written case report form. The computerized system into which the site enters the clinical trial data is generally provided and maintained by the sponsor or a third-party vendor. It is customized for each trial and may include data entry support mechanisms which validate the data against protocol and other logical requirements as the data are being entered, thus resulting in cleaner data compared to paper CRFs.
- Clinical laboratory data that are transmitted to the sponsor electronically and batch-loaded into the sponsor's database (includes other electronic data such as device data)
- Patient data that are directly captured by instrumentation
- Electronic patient reported outcome (ePRO) i.e., information that is entered by the patient directly into an electronic device, such as personal digital assistant (PDA), or directly into a web-based system
- Information that is entered by the investigator's staff directly into a computer, without first writing the data on paper (i.e., electronic source (eSource) data) and which must then be backfilled to the patient's permanent record (paper or EMR) in order to satisfy regulatory obligations.

3.2.2 The Concept of Source Data

At the center of data collection and data management for all clinical trials, regardless of the use of EDC or paper, is the concept of source data. Source data, as defined by the ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH E6) (21), are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of a trial. Source data are contained in source documents (original records or certified copies). Examples of source documents include hospital records, patient charts, laboratory notes and pharmacy dispensing records.

In clinical research, it is these source data that are transcribed onto paper case report forms (CRFs) or into the EDC system. During the trial, it is the physician's responsibility to prepare and maintain the

source data, and the sponsor's responsibility to ensure the reported trial data are accurate, complete and verifiable from source documents. To ensure the accuracy of this process, sponsors usually carry out a process called Source Data Verification, in which CRF records are manually compared to the corresponding source data in the charts. Source data are required to be under the authority of the investigator (Part 312.62(b)) and through an investigator signature on the CRFs are deemed to be accurate. The creation, modification, maintenance, archival, retrieval and transmission of data in the CRFs and subsequent manipulation, analysis and submission to the FDA are subject to the detailed regulations. Further, regulatory agencies and auditors require access to the source data in order to reconstruct a trial and ensure overall accuracy and integrity of the data. So, as electronic patient records become more common and data are recorded directly into systems (creating an electronic source, or 'eSource'), it is necessary to continue to evaluate the processes and regulations related to source data to ensure continued data integrity for clinical research purposes. CDISC's eSDI paper (19) provides an excellent overview of the current regulatory requirements applicable to source data and eSource, which we will not duplicate here. The following sections will review selected aspects of the current regulatory requirements in more detail, and further explore the concept of 'source' and 'eSource'.

Figure 2 below shows an example of data flow within EDC and associated systems, highlighting Source Data as a central component in the process.

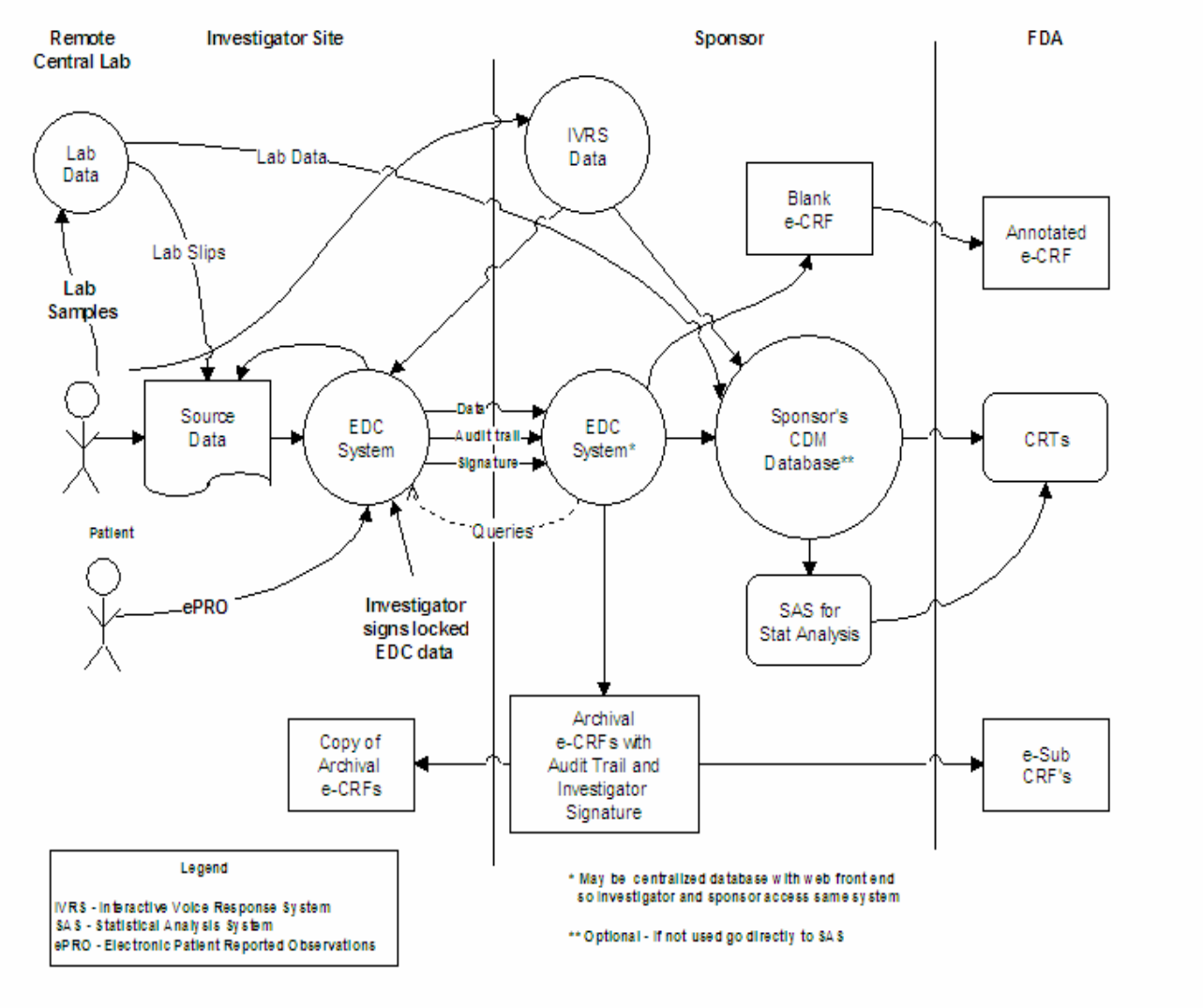


Figure 2: An Example of the Data Flow in an EDC System

From: Position Paper on Electronic Data Capture-Revision 1, PhRMA EDC Task Group (now PhRMA EDC/eSource Taskforce), 2005 (20)

3.2.3 Growth of EDC in Clinical Research

While EDC is not a new technology, its adoption by bio-pharmaceutical companies is a relatively recent effort. In the 1990's, many companies tried to deploy EDC as a pure technology solution, with only limited process changes. At the same time, the EDC vendor market place was immature and fragmented. The tools themselves were somewhat unstable and did not fully meet sponsor needs. Over time, the EDC vendor market place has matured, and while it is still fragmented, there has been significant consolidation and several market leaders have emerged. In parallel to this evolution in the market place, bio-pharmaceutical sponsors have learned that the real key to making EDC successful is to leverage the technology to redesign business processes. The result has been that EDC is no longer seen as a tool, but rather as a capability consisting of streamlined processes combined with supporting technology. Many investigative sites and bio-pharmaceutical sponsors are now using EDC to realize significant benefits in resource efficiency, data quality, and time to market. Today, EDC usage is at

steady-state in several bio-pharmaceutical companies, with many others scaling up aggressively. Overall, roughly 27-30% of all clinical trials are currently conducted using EDC, with this percentage rising year to year (4).

3.2.4 Benefits of EDC

For bio-pharmaceutical sponsors and regulators, the primary benefits of EDC include:

- Significantly reduced lag time between a patient visit and the time when the data become available for review by the sponsor. Data are accessible as soon as they are entered by the investigator site into the system.
- Timely review of accumulated data for decision-making made possible by the reduction of the data availability gap. Of particular importance is the ability to detect potential safety issues in as close to real time as possible.
- Significantly increased data quality through the inclusion of data validation checks in entry screens.
- Reduced sponsor data entry and cleaning costs.
- Database lock and delivery for interim or final analysis in a shorter timeframe by speeding up data capture and query resolution, thus offering the potential for maximizing time on patent.

EDC also delivers significant benefits for investigators and their patients:

- Provides site personnel with immediate feedback during data entry through on-line, automated checks. They are prompted to correct illogical/erroneous entries immediately, while they still have the patient's chart at hand, rather than weeks or months later as occurs with paper, thus eliminating later re-work.
- Rather than retaining large volumes of paper Case Report Forms (CRFs), at the end of the study, sites receive copies of their electronic CRF data and associated audit trail on CDs.
- Accelerates delivery of new drugs to the patients who need them by allowing study sponsors to analyze the data faster.

3.2.5 Why EDC is not the perfect answer

Unfortunately, despite these benefits, the process associated with EDC still includes some inefficiency for investigator sites:

- Despite the consolidation of the EDC market place, sponsors use a variety of EDC systems. Investigators and site staff are often required to learn how to use multiple EDC systems, and may need to have multiple computers at their sites to accommodate the various systems. The typical active investigative site is estimated to have an average of three disparate EDC systems provided by the sponsors of the clinical trials they participate in (22). In the coming years, this number may grow as the adoption of EDC by bio-pharmaceutical companies continues to increase.
- As described previously, some clinical trial data are first recorded, as part of the patient's normal care, in paper or electronic patient charts which constitute the source documents, and must then be transcribed into the EDC system. Indeed, even if the patient's charts are available at the site as electronic medical records (EMR), they cannot today be used directly for research purposes because of the variability of these systems and the fact that they generally do not comply with the regulations that govern systems used for clinical trials (see Section 3.3).
- In most clinical trials, a variable portion of the data is specific to the trial and would not normally be recorded in the patient's paper or electronic chart. For those data, the regulatory obligation to have source documents for all clinical trial data results in the need to create a separate record in addition to entering the data in the sponsor's EDC system.

- The delivery of benefits with EDC is still reliant on the site's willingness to enter data quickly and resolve any data queries in a timely manner.

Thus, a significant percentage of electronic CRF data are entered into multiple electronic and paper systems - resulting in extensive duplication of data entry and, occasionally, a lack of clarity on what was the original source. Based on current regulations, processes for the use of EDC still result in duplicative recording of data, which may explain the finding that 25% of sites surveyed (22) believe EDC is increasing their workload, despite the advantages of on-line data discrepancy management, streamlined archiving, and other tools contained within major EDC systems.

This duplication of tasks and associated costs will grow with the increasing use of electronic data sources (such as EHRs), diminishing the efficiency of both healthcare professionals and clinical research organizations. Better integration of the healthcare and clinical research environments, systems and processes can lead to further efficiency.

3.3 Current Regulatory Environment and Implications for eSource

A 2002 industry survey reported by the Electronic Data Management Forum (now eClinical Forum) indicated that clarifying the regulatory environment for EDC was one of the primary issues facing clinical research. A more recent survey reported by the Clinical Data Interchange Standards Consortium (CDISC) in 2003 confirms that the situation is unchanged with 53% of sponsors still regarding regulatory concerns as one of the main reasons for delay in the implementation of EDC (Fig 3). The PhRMA EDC Task Group position paper (now PhRMA EDC/eSource Taskforce) (20) released in 2005 highlights the regulatory issues that are problematic for EDC. Many of these issues have been addressed by the draft CSUCT guideline (13) (Sept 2004). To date this guideline has not been finalized. Some of the highlighted regulatory issues (e.g., the need to identify all computer systems used in a clinical trial, password expiration requirements, etc.) apply to the use of the EDC system as eSource; these same issues would apply to the use of the EMR/EHR system as eSource.

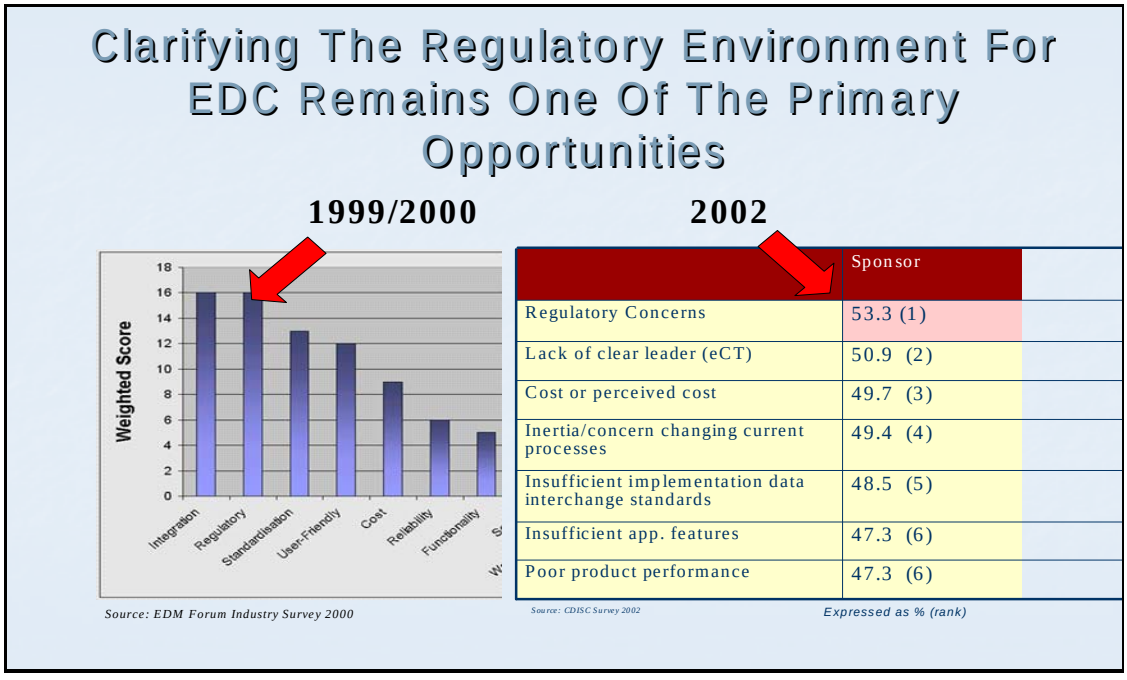


Figure 3: Clarifying the regulatory environment for EDC

3.3.1 Applicable Regulations

For bio-pharmaceutical sponsors, both the FDA and ICH provide regulations for clinical trials records and the systems and processes that maintain them. The same responsibilities of the investigator toward the accuracy of source data would exist whether data are hand-written on paper or entered and stored electronically. Clinical research source data must follow the ALCOA principles[5]. If they are entered and stored into an EMR/EHR or EDC system as the sole source, then that system must be compliant with these regulations as well.

Applicable regulations are:

- U.S. FDA, 21 CFR 312.62(b) Investigational New Drug Application: Investigator recordkeeping and record retention
- U.S. FDA, Guidance for Industry, Part 11, Electronic Records; Electronic Signatures, and Guidance on 21 CFR Part 11 Scope and Application
- U.S. FDA, Guidance for Industry-Computerized Systems Used in Clinical Trials (CSUCT)
- ICH, E6 Good Clinical Practice: Consolidated Guidance

In parallel to the FDA regulations, a number of privacy laws and regulations exist. For the United States, this is HIPAA (American Health Insurance Portability and Accountability Act), which is a set of rules issued by the US Department of Health and Human Services. HIPAA ensures that all medical records, billing and patient accounts are compliant with regard to documentation, handling and privacy. The three major rules (privacy, transaction and code set, security) have had a major impact on the EMR industry. For the bio-pharmaceutical industry, these rules will mostly affect online marketing, and medical research handling of patient's personal and health information. In the EU, Canada and other countries, similar privacy protection legislation exists within each country.

An example of privacy protection legislation can be seen in the U.S. HIPAA regulations, codified in:

- 45 CFR 46 (Basic HHS Policy for Protection of Human Research Subjects)
- 45 CFR 160 and Subparts A and E of Part 164 (standards for Privacy of Individually Identifiable Health Information, the Privacy Rule)

3.3.2 Challenges for using Electronic Health Records as eSource

If source data for clinical research are collected electronically in EMR/EHR systems, one can expect that the requirements for compliant electronic systems as described above will extend to these systems, leading to a number of practical challenges that will have to be overcome. The intent of the following sections is to start exploring the current gap between the realities of EMR/EHR data and existing regulatory requirements pertaining to clinical research.

1. Data collection processes at the point of care are minimally controlled – 21 CFR Part 11 issues

Healthcare is under tremendous time and cost pressure. Patient records predominantly serve the purpose of documenting and facilitating the management of individual patient care delivery. EMR/EHR systems are optimized toward this purpose. It would be inefficient and costly for a hospital or physician's office to carry out the meticulous documentation processes that are common in the bio-pharmaceutical industry.

If data in EMR/EHR systems are used as eSource for clinical trials, authority checks (as expected under 21 CFR Part 11) will have to be applied to ensure that only authorized persons can access the system, and

[5] ALCOA: Attributable, Legible, Contemporaneous, Original and Authentic (CSUCT Guidance (13))

an electronic audit trail will be required. This may collide with practices such as generic user names or passwords shared by multiple staff, particularly in small physician's offices. It will also create the need for a substantial redevelopment of the EMR/EHR products on the market, especially for those that do not have clinical research-compliant audit trail capabilities today. The enforcement of a requirement such as audit trails may cause adoption or utilization challenges, resulting in a slower adoption curve if not given appropriate encouragement and incentive.

2. Source data are far from perfect – CSUCT ALCOA and ICH GCP issues

Patient data are collected mostly when medical treatment is necessary. Depending on the circumstances and nature of the condition, the quality of the records may suffer substantially. For example, in emergency situations, the medical staff of ambulances and emergency rooms will exclusively focus on rapid intervention rather than accurate record keeping. In addition, recordings are made by a variety of staff of different qualifications: physicians, nurses, phlebotomists, etc. In the medical practice, these shortcomings are usually mitigated when the physician responsible for the treatment produces a discharge summary. All data are then subject to professional judgment and a representative selection of the key data are provided. The question as to what is the source data then needs to be tackled: Should the notes from each of the consecutive caregivers be considered source data or is the summary from the overseeing physicians the only valid source data? This ambiguity was acknowledged by the FDA's Division Scientific Investigation (DSI) representatives, who met with the PhRMA EDC/eSource Taskforce in January 2006. They noted that the regulations do not equate source data with initial data.

This piece-meal record-keeping approach is notoriously flawed and leads to a great number of treatment errors (6). In fact, the improvement of this situation and easy accessibility to the information is one of the reasons for the introduction of the EMR and EHR systems. However, without process and control changes similar to clinical research controls, the goal of improving the accuracy of healthcare information may remain an elusive one.

3. Control and ownership of data is difficult to clearly identify – 21 CFR Part 312.62(b) issues

Since the investigator is responsible for keeping records of the case history of the patient (11), it is inferred that the sponsor must not have exclusive controls of these records.

The FDA's current position on sponsor hosting of such eSource data is defined in the Feb 2006 Draft Guidance on Patient Recorded Outcomes (23, page 26). This guidance states that the sponsor must not have exclusive control of the source document, there must not be only one database, and the investigator must be accountable for the accuracy of the data.

Current EDC systems, however, are often hosted by the sponsor or third party over the public internet. If such EDC systems or modules develop into or integrate with EMR/EHR systems, this model would no longer be viable, as it would make the sponsor the custodian of the sole dataset.

3.4 Data Standardization Initiatives

The emergence and evolution of marketed EHR and EDC systems have been completely separate. While these systems both function as electronic clinical record keepers, they are not interoperable. Only recently have organizations like HL7, representing healthcare data standards, and CDISC, representing research data standards, participated in collaborations to work toward standards to support interoperability and facilitate integration.

In this section, we describe several standards initiatives; we acknowledge, however, that there are other organizations focusing on this area. As is obvious by the number of standards organizations and the long period that some of these have been in existence, this is not an area that is easily defined or agreed upon. In order for electronic health records to be shared among different healthcare providers and/or clinical research, it is critical that a core group of standards are agreed upon globally and implemented. In the mean time, technology solutions will have to adjust for the lack of standardization.

Descriptions of the following standards initiatives have been acquired from their websites, which are listed in section 9.2.1.

3.4.1 Healthcare Data Standards: Health Level 7 (HL7)

Health Level Seven (HL7) is a global, non-profit organization started in 1987 that produces standards for clinical and administrative data. "Level Seven" refers to the highest level of the International Standards Organization's (ISO) communications model which supports such functions as security checks, participant identification, availability checks, exchange mechanism negotiations and data exchange structuring.

HL7's mission is to create standards for the exchange, management and integration of electronic healthcare information, to promote the use of such standards within and among healthcare organizations, and to increase the effectiveness and efficiency of healthcare delivery for the benefit of all. In 2002, the HL7 EHR Special Interest Group was established with the mission of designing standards to support the exchange of information for clinical decisions and treatments, and help lay the groundwork for nationwide interoperability by providing common language parameters that can be used in developing systems that support electronic records.

3.4.2 Research Data Standards: Clinical Data Interchange Standards Consortium (CDISC)

In the bio-pharmaceutical industry, CDISC, begun in 1997, is an open, multidisciplinary, non-profit organization that has established worldwide industry standards to support the electronic acquisition, exchange, submission and archiving of clinical trials data and metadata for medical and bio-pharmaceutical product development. The mission of CDISC is to develop and support global, platform independent standards that enable information system interoperability to improve medical research and related areas of healthcare.

3.4.3 Joint CDISC / HL7 Charter

In 2001 a partnership was formed between CDISC and HL7 and a Clinical Trials Special Interest Group (CT-SIG). In 2004, FDA joined HL7 and CT-SIG was elevated to a Regulated Clinical Research Information Management (RCRIM) Technical Committee. The shared goal of CDISC, HL7 and FDA is to have one overarching standard model for data interchange for healthcare information and clinical trial/clinical research data and to produce models harmonized to yield value for both clinical research and healthcare.

RCRIM's mission is to develop standards to improve or enhance information management during research and regulatory evaluation of the safety and efficacy of therapeutic products or procedures worldwide. This committee intends to facilitate the development of common standards for clinical research information management across a variety of organizations (including government agencies (FDA, CDC, and NIH), private research efforts, and sponsored research) and thus improve the

availability of safe and effective therapies by improving the processes and efficiencies associated with regulated clinical research.

In 2004, CDISC conducted a proof-of-concept that demonstrated the joint application of the HL7 Clinical Document Architecture (CDA) and the CDISC Operational Data Model (ODM) to allow for single data entry into an electronic CRF with subsequent population of an EHR and an operational clinical research database. This was called Single Source Proof-of-Concept. In 2005, CDISC, HL7 and NCI successfully mapped the ODM to the HL7 Reference Information Model (RIM). The ultimate goal is a single overarching data model to support both clinical research and healthcare (25).

3.4.4 Biomedical Research Integrated Domain Group (BRIDG)

The Biomedical Research Integrated Domain Group (BRIDG) is an open model collaboration between CDISC, HL7, National Cancer Institute (NCI), FDA, and others to develop a model to support standards within the clinical research domain. This domain-analysis model is being developed to support the harmonization of standards within and between clinical research and healthcare to enable the development of useful technology solutions in these domains that will be interoperable.

3.4.5 Healthcare Information Technology Standards Panel (HITSP)

The Healthcare Information Technology Standards Panel (HITSP) is sponsored by the American National Standards Institute (ANSI) in cooperation with strategic partners such as the Healthcare Information and Management Systems Society (HIMSS), the Advanced Technology Institute (ATI) and Booz Allen Hamilton and funded by a contract award from the U.S. Department of Health and Human Services.

The Panel is comprised of members from standards development organizations (SDOs), non-SDO stakeholder organizations (e.g., clinicians, providers, health IT vendors, research organization, and national organizations with an interest in healthcare information technology standards), governmental bodies, and consumers.

The Panel's objective is to achieve widely accepted and readily-implemented consensus-based standards that will enable and support widespread interoperability among healthcare information technology, especially as they would interact in a Nationwide Health Information Network (NHIN) for the United States.

3.4.6 *open*EHR Foundation

The *open*EHR Foundation, established in 2003, works in an open manner, based on active relationships with domain experts and users, with national and international standards bodies, including ISO, CEN (Comité Européen de Normalisation), and HL7, with software and system developers, and with educational institutions and researchers.

The *open*EHR Foundation is committed to supporting relevant government-sponsored and industry-based standards bodies as a means of encouraging the widespread and effective adoption of interoperable EHRs.

3.4.7 Certification Commission for Healthcare Information Technology (CCHIT)

The Certification Commission for Healthcare Information Technology (CCHIT), established in 2004, is the recognized US certification authority for electronic health records and their networks, and an independent, voluntary, private-sector initiative. Their mission is to accelerate the adoption of health information technology by creating an efficient, credible and sustainable product certification program.

3.4.8 Integrating the Healthcare Enterprise (IHE)

Under the leadership of HIMSS and the Radiological Society of North America (RSNA), IHE began in 1998 as a collaborative effort to improve the way computer systems in healthcare share critical information**.** Today IHE has sponsors and supporting organizations in North America, Europe and Asia. IHE is an initiative by healthcare professionals and industry to improve the way computer systems in healthcare share information. IHE promotes the coordinated use of established standards such as Digital Imaging and Communications in Medicine (DICOM) and HL7 to address specific clinical needs in support of optimal patient care.

IHE follows a defined, coordinated process for standards adoption. They do not create new standards. The process steps are to 1) identify interoperability problems, 2) specify integration profiles, 3) test systems at the annual IHE Connectathon, and 4) publish integration statements for use in RFPs (request for proposals).

3.4.9 Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT)

SNOMED CT is a dynamic, scientifically validated clinical healthcare terminology and infrastructure that makes healthcare knowledge more usable and accessible. The SNOMED CT Core terminology provides a common language that enables a consistent way of capturing, sharing and aggregating health data across specialties and sites of care. Among the applications for SNOMED CT are electronic medical records, ICU monitoring, clinical decision support, medical research studies, clinical trials, computerized physician order entry, disease surveillance, image indexing, and consumer health information services. SNOMED CT has been recognized by the many standards setting organizations and government bodies, including a recommendation by Consolidated Health Informatics (CHI), the US initiative charged with defining dictionary standards for the national EHR.

While SNOMED CT is the recommended dictionary for the US EHR, the bio-pharmaceutical industry prefers to use an alternative medical terms dictionary, MedDRA, which is more suitable for research needs.

3.4.10 MedDRA

The Medical Dictionary for Regulatory Activities (MedDRA) is a pragmatic, medically valid terminology with an emphasis on ease of use for data entry, retrieval, analysis, and display, as well as a suitable balance between sensitivity and specificity within the regulatory environment. It was developed by the International Conference on Harmonisation (ICH) in the early 1990s and is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) acting as trustee for the ICH steering committee.

MedDRA terminology applies to all phases of drug development, excluding animal toxicology. It also applies to the health effects and malfunction of devices. Major global regulatory authorities in the United States, Europe, and Japan are adopting MedDRA and moving toward requiring its use.

3.4.11 Laboratory Logical Observation Identifier Name Codes (LOINC)

Laboratory Logical Observation Identifier Name Codes (LOINC) is a voluntary effort housed in the Regenstrief Institute for Healthcare, an internationally respected non-profit medical research organization associated with Indiana University. LOINC system was initiated in 1994 by the Regenstrief Institute and developed by Regenstrief and the LOINC committee as a response to the demand for electronic movement of clinical data from laboratories that produce the data to hospitals, physician's offices, and payers who use the data for clinical care and management purposes.

The LOINC laboratory terms set provides a standard set of universal names and codes for identifying individual laboratory and clinical results. LOINC codes allow users to merge clinical results from many sources into one database for patient care, clinical research, or management.

3.4.12 Consolidated Health Informatics (CHI)

The Consolidated Health Informatics (CHI) initiative is one of the Office of Management and Budget's (OMB) eGov initiatives. CHI is a collaborative effort in the US to adopt health information interoperability standards, particularly health vocabulary and messaging standards, for implementation in federal government systems. About 20 department/agencies including the Department of Health and Human Services, the Department of Defense and the Department of Veteran's Affairs are active in the CHI governance process.

CHI adopted 20 uniform standards for electronic exchange of clinical information to be used across the federal health enterprise in 2004. Currently CHI is focusing on implementation and maintenance of adopted standards and identification and adoption of new standards.

3.5 Overview of eSource Initiatives

Despite limitations as noted in previous sections such as an unclear regulatory environment and the lack of accepted standards across all regions and platforms, groups are still interested in finding ways to use eSource within the current environment. To provide a clearer picture of the convergence of the environments for electronic healthcare and electronic clinical data capture, it is necessary to outline some current eSource pilots. While a few are described below, we recognize there may be many more that have not yet been publicized.

- Eli Lilly conducted a clinical trial in late 2001/early 2002 entirely over the Internet (32). All data were collected over the internet from patients and from site personnel into the electronic record for the patient and became the patient's electronic record. This was hosted by a third party and the study design was agreed by the FDA. Depersonalized data were transferred to Lilly for statistical analysis and reporting. The website will be maintained for the duration of the data retention period. It is believed that this is one of the first trials conducted under an IND to be completely run over the Internet. One of the criteria for enrolment was that the patient has a home computer that could access the website. It was not clear how this might have biased the patient population selected. While demonstrating that such trials are feasible and can be compliant with regulations, there is still the problem for an investigator who works with several sponsors, each having a different electronic record database to maintain – all separate from the investigator's non-clinical trial patient records.
- Johnson & Johnson (J&J) is performing Phase I trials using tablet PCs (10). This allows the investigator to move around the clinic/hospital and collect the data directly as they are generated.

J&J are using the tablet PCs much like any other EDC system except that the mobility makes it easier to enter data directly and thus eliminate a separate source. The data entered into the tablets do not reside there, but go directly to a local, on-site server. Data are then transmitted from the local server to the sponsor's (J&J's) central server.

- Pilots involving retrospective mining of data to be used for analysis to determine trends and information for future clinical trials were reported by the Karolinska Institute (28). In these pilots, large amounts of data were retrieved from pre-existing electronic medical records databases and analyzed in a short timeframe. Although these pilots used retrospective collection of data, they did demonstrate that transfer of eSource data to a sponsor for clinical trial analysis is feasible and also that efficiencies can be seen using this process. Since the collection was an export from the EHR, the medical records holder could control that only depersonalized data were exported and protect patients' privacy. See section 3.2 for a description of retrospective data mining.
- Siemens Medical Solutions, an EMR vendor, is currently conducting a pilot with the Technical University of Munich which includes backend integration, enabling the automatic transfer of data from electronic medical records into an EDC system (24).
- CDISC conducted a proof of concept pilot (called "Single Source") using standards for healthcare information (HL7) and standards for clinical research (CDISC) for the electronic source documentation of clinical trial data and the generation of medical records for patient care from a single point of entry. This takes the approach of an entry application prior to either EMR or EDC systems in which both patient data and clinical research data enter under regulatory control and from there are populated to the appropriate databases (25).
- Lundbeck Pharmaceutical is allowing eSource into their EDC systems by creating a controlled PDF copy of the data as it is saved or updated and automatically storing this PDF off-site in a secure facility outside the sponsor's direct control (i.e., controlled by a trusted third party). These controlled PDFs may be viewed but not modified or overwritten by both the sponsor and the site and used to verify data integrity should any questions arise. In this way, the sponsor has access to the data immediately, yet there is still a separate source for verification. These measures are taken in order to meet current regulatory guidelines (26).

Regulatory agencies are also showing interest in furthering eSource as demonstrated during the January 11th, 2006 meeting between CDER's Division of Scientific Investigations and the PhRMA EDC/eSource Taskforce. At that meeting, DSI representatives expressed their interest in exploring eSource options and associated issues. They also stressed that investigator's control over the source data—whether it is maintained in paper records or electronically—remains a fundamental requirement.

These recent initiatives demonstrate that there is bio-pharmaceutical industry interest in further exploring the potential of eSource and this is supported by the CDISC survey data which overwhelmingly indicates that there is such interest. As vendors, sponsors and regulatory agencies work out the issues surrounding the use of eSource, we will move closer to the vision of having the variety of data collection systems currently in use being able to directly share data for a variety of purposes (e.g., healthcare and clinical trials).

4 IDEAL FUTURE ENVIRONMENT

4.1 The Challenge

The eHealth initiatives thus far have been primarily focused on healthcare delivery and payments and have not been considering the requirements of secondary users of healthcare data such as clinical researchers. This omission has occurred despite the desire of regulators to speed up delivery of new medicines, reduce the cost of new and improved treatments and deliver improved patient care based upon best practices.

Significant benefits can be accrued through collaboration of both the healthcare and research worlds in effectively and efficiently sharing data. Without such collaboration, as the use of EMR/EHRs grows, both the healthcare sector and the bio-pharmaceutical companies will be obliged to spend valuable resources on duplicate tasks. The challenge is to develop systems and processes that will allow the direct use of patient electronic medical data for both prospective and retrospective clinical research[6] in a way that meets data protection, regulatory and ethical research requirements. For purposes of this paper, we are using the term "EHR/CR" to mean a system that is capable of supporting both electronic healthcare and electronic clinical research data capture. In meeting this challenge, four areas will need to be addressed:

- A mechanism for satisfying regulatory and clinical research requirements for system validation and data reliability will need to be created, or adapted from existing clinical research systems
- Data standards for electronic data collection, interpretation, and exchange will need to be determined based upon needs of both the medical and clinical research communities.
- Controlled, secure processes for releasing and transferring data from and to EHR, device and research systems will need to be developed, consistent with personal data privacy, clinical trial regulations and bioethical considerations.
- The ability of the research community to contribute toward a EHR/CR that would satisfy its needs without compromising healthcare's need to follow any anti-kickback regulations (e.g. US Stark legislation) or have direct ties toward specific bio-pharmaceutical manufacturers.

The transition from disparate systems to a truly integrated EHR/CR environment is likely to be an evolutionary process that occurs over a number of years.

4.2 Attributes of the Ideal Environment

The ideal future environment for the capture and exchange of electronic data for clinical trials includes attributes that would be part of a quality nationwide (or global) network of interoperable patient health records with additional requirements for the use of these records for clinical trials. Following is a list of requirements needed for a successful EHR/CR system. It includes requirements that we assume would already be a part of a nationwide (or global) EHR network, followed by requirements that would be specific to the needs of collecting clinical research via this standard EHR. It should be noted that interim solutions toward this ideal goal (such as investigators using certified, standard EHR systems) will also have benefit. Some interim solutions are discussed by the CDISC Electronic Source Data Interchange (eSDI) paper (19).

4.2.1 System and System Design

Requirements for a successful nationwide (or global) eHealth network:

[6] See discussion of prospective and retrospective clinical research in Section 3.2

- Widespread use of certified EHR systems (that comply with defined data standards and agreed regulatory standards)
- Systems will be certified via a formal accreditation process (e.g. similar to what is currently available for lab systems)
- EHR will share common data standards and features such that data can be interchanged
- The EHR system must be non-intrusive to the doctor-patient relationship
- The performance and reliability of the individual EHR systems must be very high
- Access points must be secure
- System must be easy to use by different types of staff (physicians, nurses, other healthcare providers, administration, even patients)
- Physicians and other healthcare providers must be able to use the EHR system to access centrally collected data (labs, ECG, etc.)
- Potential privacy issues must be managed
- Direct data transfer mechanism/protocol from medical devices must exist such that this information can be part of the patient's EHR
- Access to patient electronic records is available at every location where a patient is seen (e.g. physician's office, hospital, lab, etc.) to avoid the creation of paper records and subsequent entry of this information

Additional requirements for EHR/CR:

- A portion of the EHR system must be able to collect all required research data and provide support for clinical research workflow at the investigator site. Once a patient signs informed consent for a clinical trial, then additional trial screens and information would appear when that patient's records are accessed
- Systems must be compliant with regulatory research requirements (e.g. access control, audit trail, backup, validation, and ALCOA properties)
- Regulators must accept data sourced from EHR systems that have been accredited for research purposes
- System must differentiate and handle both clinical trial patient data and private patient data.
- Study sponsors can receive/review only the parts of the patient's data that are relevant to the clinical trial
- Data security methods preserve requirements for data blinding for both sponsor and investigator
- The source of data within the system is clearly indicated
- An accepted process is available to approve research access to EHR data in a way that meets data privacy and bioethical considerations
- Chain of custody (i.e. who is responsible for data at different points) is managed

4.2.2 Data Standards

Requirements for a successful nationwide (or global) eHealth network:

- Accredited data and interchange standards are agreed on and adopted
- Translation requirements are minimized through the use of standard templates and dictionaries (rules for dictionary use limit untranslatable text information)
- Standards should be affordable and globally available
- Standards cannot assume that all sites (countries) have a top level (or the same level) of technology

Additional requirements for EHR/CR:

- Standards for both Bio-pharmaceutical and eHealth initiatives converge such that common data exchange standards allow for flexible data interchange between EHR and clinical research systems
- Common data standards are adopted extensively across clinical research sponsors

- A digital identity standard that allows organizations to meet the requirements of document authentication, legally binding digital signatures, integrity, uniform liability controls and privacy (e.g., SAFE Initiative)

4.2.3 Quality System

Requirements for a successful nationwide (or global) eHealth network:

- Formal accreditation process for EHR systems allows confidence in system compliance toward data integrity and security
- Disaster recovery and contingency plans for the event of system unavailability

Additional requirements for EHR/CR:

- eSource through use of EHR must be part of a system with appropriate validation and built-in security and audit features and under system life cycle control
- Record showing investigators have completed training on responsibility and accountability for the integrity of the data, and system functionality and SOPs

4.2.4 Regulations

Requirements for a successful nationwide (or global) eHealth network:

- Applicable privacy regulations and healthcare delivery regulations will be met for reviewing and transferring data within and between countries

Additional requirements for EHR/CR:

- Changes required in regulations/regulatory positions to accommodate eSource (e.g. 21 CFR Part 11, CSUCT) (See section 3.3)
- EHR systems required to meet yet-to-be-determined regulatory guidance for e-source as well as 21 CFR Part 312.62(b), ICH E6, 21 CRF Part 11, and CSUCT

4.3 The Vision: EHR/CR System

In order to streamline the capture of clinical trial data and to realize associated economic and time savings, redundant data collection must be eliminated and communication between the sponsor and investigator sites must be clear, non-redundant, timely, and effective. Such a framework will allow data exchange in a manner compliant with both data protection and other research specific regulations and will lead to innovative and efficient methods for data collection and data use.

Following is one possible scenario of what *might* be possible as technology in both the Bio-pharmaceutical and Healthcare industries evolve and merge. *This is not a recommendation, but rather an example for illustration and to foster discussion.*

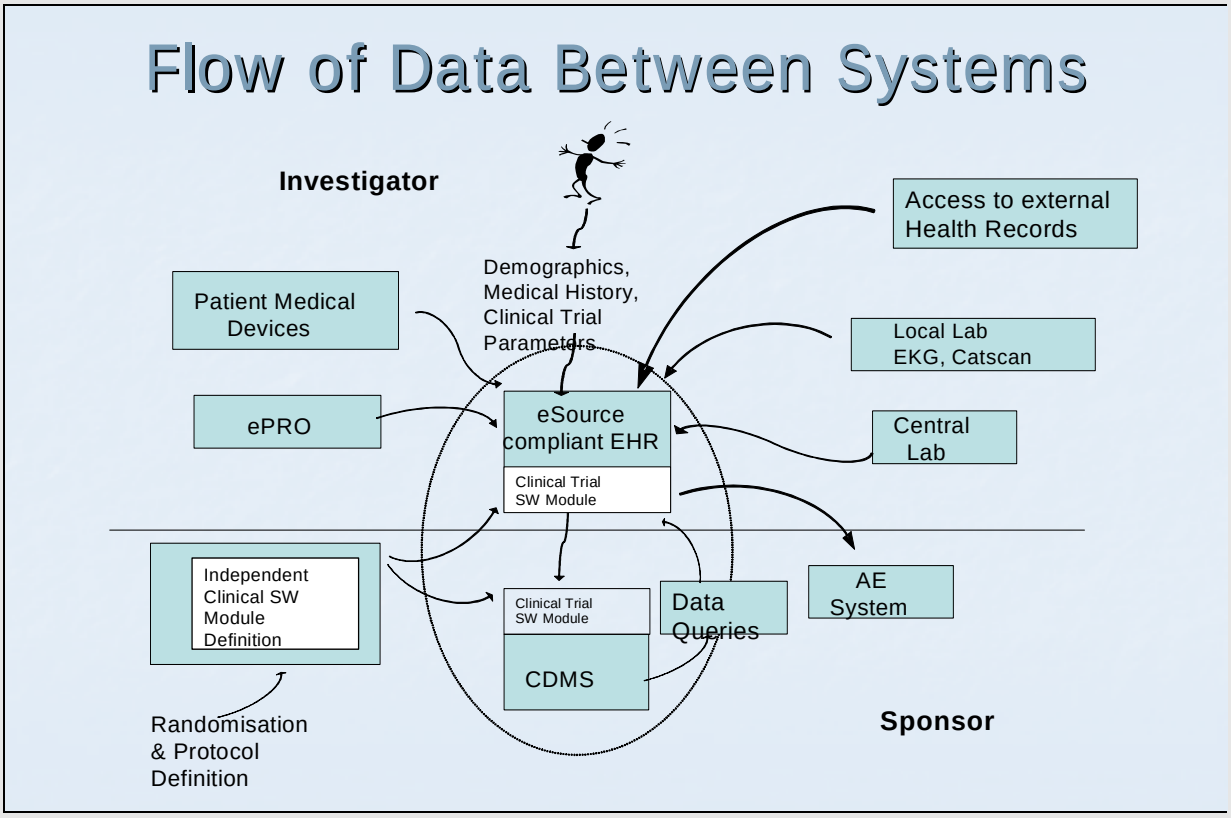
Possible Future Scenario

Patients are being seen at hospitals, clinics and private practices in many countries, and the health information is being entered and retrieved from computer databases during these visits. At the same time, within a pharmaceutical company, a clinical study is being planned. The clinical study protocol parameters are entered into a standard form or program and distributed electronically for approval. Once approved, the study sponsor will tap into the national eHealth system to identify potential investigators who may have a pool of appropriate patients. This survey is accomplished through data mining of non-patient-identified information available to researchers. Based on this survey, physicians are approached and asked to become investigators. The physicians can then query their own patient databases to determine if they do have suitable patients and if they want to become involved in the study.

Back at the pharmaceutical company, these study parameters are used by a program (possibly vendor-provided) to set up the data capture system and database for this study. It will utilize a library of standard data elements and

associated edit checks that has been previously set up and augmented over time. Once all standard database tables, data entry screens and validation checks have been set up and approved, necessary validation on the study screens and database structure is performed.

The study is now ready to be deployed to the study investigators. It is in the form of an independent software module that employs standard interface definitions developed by a standards committee within the Bio-pharmaceutical and Healthcare industries. Using the standard interface definitions, the independent clinical module can be recognized by any certified electronic health record (EHR) system being used by the investigator sites. When the investigator staff receives the module for the new study, it is installed and a self-check program runs to verify that it is working properly, and logs the results. These results are automatically transmitted to the study sponsor for storage with the validation documentation for that study. This constitutes the technical qualification of the site and signals to the sponsor that the site is ready to enter clinical patient data for this study as soon as all other site initiation steps are completed (e.g., regulatory document filing, IRB approval, etc.).



Since the clinical module is being run by the EHR system already in place at the investigator site, it has the same look-and-feel they are already accustomed to. Apart from training on the clinical protocol, there will not be any need for individual staff training of the clinical system. While the data collected for each study will be different, the behavior of the EHR system will not. Since the EHR system is already integral to the daily routine of the investigator site, the clinical trial is not adding a new layer of complexity or work. When a patient comes into the practice, information not originating from the practice is accessed through a standard method that is available to all healthcare sites (e.g., national network, smart card, memory stick, etc.). The investigator staff will have access to the patient's entire history, regardless of where the care was given. Any third party diagnostic parameters (such as lab test or x-ray results, patient diary data) will also have been received and stored in the EHR system such that it is readily available to the investigator. The staff will enter all information pertinent to this patient visit. If the patient is also on a clinical trial, additional information and screens will be displayed to prompt the staff to collect the additional information and to assist with scheduling and patient visit reminders. While the data are being collected, any possible validation checks are done such that they can be corrected in real-time if necessary. Upon investigator release, data will be immediately available for review by the sponsor. At the sponsor site, any additional data validation checks and medical monitor review will be performed. Any resulting queries will be sent back to the investigator for review and resolution.

The clinical trial patient data will physically reside in both the EHR system and the sponsor's analysis database. Only the EHR system's clinical data module will be considered the source, and it must stay in a validated state under the control of the investigator. Security features surround this module such that it is in compliance with all regulations pertaining to clinical data. At the end of the study, data from this module will be archived in a standard format (perhaps XML or PDF) such that it can be easily read by the investigator and/or an auditor in the future, using standard tools, if need be.

Figure 3: Potential Future Scenario Story

5 BENEFITS AND BUSINESS IMPACT FOR STAKEHOLDERS

This section highlights the benefits and potential business impact that could be realized through a combined EHR/CR system in which clinical research data could be collected and stored with the same mechanism used for other patient data. Section 5.6, Potential Roles and Responsibilities with EHR/CR is provided as food for thought on how roles and responsibilities could be affected.

EDC as currently adopted in about 27-30% of clinical trials provides acknowledged benefits over paper CRF data capture. Since a significant portion of the clinical data (e.g., medical history, medical procedures, prescribed medications, vital signs) needed for the trial will already be available in an electronic form through the EHR, the introduction of the EHR/CR technologies and processes will extend and accelerate the existing benefits of EDC into an increasingly higher number of clinical trials, and an increasingly higher number of hospitals and healthcare clinics. Additionally, more physicians could become involved in clinical research, one major hurdle to participating in clinical research, clinical data capture, will already be overcome by those facilities that have adopted EHR systems that include EHR/CR technology.

Necessary business process changes will affect all involved in clinical research. We envision that the healthcare centers involved in clinical research and clinical trial participants will benefit the most through improved patient safety. Clinical sites will be able to devote quality time to their patients and not be distracted by sponsor-supplied EDC systems that do not fit their common practices. Trial sponsors, CROs, regulatory agencies, and other stakeholders will also benefit. It is therefore advantageous for the bio-pharmaceutical industry to become an important participant in the development of EHR and in particular EHR/CR technologies.

5.1 Patients

All patients whose healthcare provider participates in a nationwide EHR system will reap benefits of that system facilitating clinical research. These benefits are:

- Potential to address underserved populations through clinical trial recruitment and participation
- Greater possibility of being identified for a clinical trial because their physician will have better ability to search his/her patient population for inclusion criteria
- New therapies get to market and reach patients faster due to more efficient clinical research process
- Higher data quality leads to better safety

In addition, patients participating in a clinical trial will see more immediate benefits. Because no transcription of data to an EDC system is required, all clinical trial safety data relating to the patient will be immediately available to their physician, the medical monitor and the sponsor, allowing safety issues to be identified in real time. Additionally, the sponsor will be able to easily pool data in real-time across multiple geographies, racial and ethnic populations

(prospectively or retrospectively), and pool safety data on drugs and drug classes of compounds, allowing possible drug interactions to be detected sooner.

Clinical trial patients' benefits:

- Improved safety monitoring on an individual trial basis as well as longer term (pre-approval and post-approval)
- In Phase IV safety trials on approved, marketed drugs, the sponsor could look across a larger number of patients and more easily identify less frequently observed unexpected adverse events
- Potential for improved patient-physician interaction due to efficiency of process in investigator's office leading to a less hurried timeslot
- Patient's health records offer a complete picture of all patient events including clinical trial information

5.2 Investigator Staff

For sites and investigators, data contained within their patients' database can be used to identify those who may benefit the most from a new therapeutic drug or device. Trial-specific inclusion and exclusion criteria will be readily assessed. Additionally, clinical sites benefit as collection of data required for clinical studies will be incorporated within their daily work routine. Essentially, as sites see patients who are participating in a clinical trial they will use the same computerized systems adopted by their practice to enter data, address queries, report any safety concerns and adverse events and schedule trial-specific visits and procedures. EDC has already introduced many benefits as well as positive process changes that would increasingly be seen in more investigational sites.

Clinical / investigational site benefits:

- Patient recruitment – EHR records could be searched for patients satisfying inclusion/exclusion criteria. The assumption is that EHR systems will have the capability to define criteria for selection of patients (e.g., disease, severity, medications taken, medical history, and specific vital signs such as blood pressure)
- The time required to check-in a patient and complete the medical record will be significantly reduced:
  - Data entry will be simplified and more efficient due to a one-time data entry into the EHR system (instead of today's multiple entries) and improved record retrieval
  - Direct transfer of validated data to research systems will be simplified and more efficient due to a common validated interface
- Information storage will be more efficient as data will be stored electronically saving on space requirements currently needed for paper trials and/or multiple trial/sponsor hardware
- Serious adverse event (SAE) reporting and management may be simplified and improved as SAEs and associated relevant information, maintained within the EHR could be sent to the sponsor. The sponsor could have the capability to obtain information pertinent to the outcome and causality of the SAE by having real time ongoing access specific to the SAE enabling them to prepare a comprehensive narrative.
- Regulations and controls surrounding clinical data capture can improve overall quality of all data managed by the EHR system
- Potential to perform more trials with same level of in-house resource due to efficiency in trial management

- Investigators will access their data through the use of a single and familiar EHR rather than through different sponsor/vendor developed front-ends, reducing training and ongoing support issues
- Efficiency in presentation of patients' entire medical history, including data from clinical trial participation
- Standards will enable data collection and integration to be more consistent and investigators will have a common understanding with regard to data definitions and format when dealing with multiple sponsors

5.3 Government-Sponsored eHealth Initiatives

Collaborative efforts between government, bio-pharmaceutical Companies and other clinical research bodies (e.g., academia, National Cancer Institute (NCI)) will be increasingly possible with the establishment of nationwide electronic health records. Processes need to be established to ensure that government and the clinical research community can work together to identify national and global healthcare issues that need to be addressed. Access to patient data will be readily available for both prospective and retrospective analysis. This will enable identification of future healthcare needs and has the potential to address those needs before they become urgent.

Benefits for government sponsored initiatives:

- Potential for bio-pharmaceutical industry to assist in funding of national eHealth initiatives
- Improved population health through improved clinical research processes leading to better understanding of emerging population health needs
- Facilitation of getting new therapies to market faster

5.4 Regulatory Authorities

Auditing clinical sites (i.e., comparing source data with that provided by the sponsor), evaluating sites for potential fraudulent activity, and early monitoring for safety issues will be made easier with a national EHR/CR system. A key responsibility of regulatory authorities is ensuring that the data provided to support approval of a new drug or medical device truly represents that collected at the clinical site. Regulators have had concerns with electronic data capture, in particular electronic source, if that source data is maintained by the sponsor. The FDA Division of Scientific Investigation (DSI) has stated that there must be two independent data sets, one maintained by the investigator and one maintained and submitted by the sponsor. Regulators want to ensure that data can be audited. With an EHR system that is under the investigators' control, data is independent from the sponsor's study data and will be readily available for comparison.

Benefits for regulatory authorities:

- With a nationwide network, regulatory authorities could have the capability to review and audit sites' electronic source data against the data provided by the sponsor, thus reducing the need for actual site visits by auditors while giving more transparency to the authorities
- Refocus workload – the reduction of paperwork will allow for auditors to focus more on key areas
- Facilitated audit trail – standard audit trail information for review with a submission

5.5 Sponsor / Bio-pharmaceutical Industry

The bio-pharmaceutical industry has already benefited from the use of EDC and EDC processes in studies where this technology has been possible. With EHR/CR, the sponsor will see the EDC benefits in an increasing number of trials. In addition, they will benefit from better availability to

target patient populations. Because the sponsor's data comes directly from the source (i.e., the EHR), queries will be kept to a minimum and source data verification will be reduced or eliminated. The process for conducting clinical trials and collecting patient data will evolve into one that is more collaborative with the practices of the investigational site. Additionally, this will ensure compliance with 21 CFR 312.62(b): Investigator recordkeeping and record retention.

When standard clinical research requirements/functions are built into EHR systems, development and support of today's EDC systems will go away. This has the potential to lower the cost of clinical research and enable a greater number of clinical trials and sponsors to participate. In general, redundant systems and overhead are eliminated.

Benefits for bio-pharmaceutical sponsors:

- With the ability to compare safety data from a clinical trial to a much larger baseline (i.e. all EHR patients), there is a potential for improved analysis and projection of long-term safety. This can be accomplished through the sponsor's ability to do large retrospective trials to identify potential safety issues or review post-market product use, via access to information on patients who are using these products. Such retrospective trials would need to be in compliance with patient privacy regulations. New regulations may be required to address how aggregate data can be accessed and by whom.
- Better access to target patient populations
- Ease of study execution:
  - Utilization of standardized EHR/CR components
  - As data transferred to research is a transaction copy of the source data no source data verification (SDV) will be required and queries will be reduced
- Eliminates redundant computer systems and overhead:
  - Application and hardware support, helpdesk, and training will be reduced
- Archiving requirements will be significantly reduced:
  - More of the Trial Master File will be electronic
  - Sites will already hold research data (as source) therefore preparation of an archive copy for retention at the site may not be required
- Pharmacy and patient records will be integrated within the EHR environment allowing drug accountability to be performed electronically via electronic access to dispensing and usage, monitoring of supplies, automated ordering, etc. Randomization to treatment would be handled external to the EHR
- Transcription errors are reduced or eliminated
- EHR/CR will lead to improved efficiencies with regard to time saving and can contribute to reduced cost in clinical trial execution. This will be achieved through elimination of redundant processes
- Collect data in a format that lends itself to integration for submission
- Potential to reference data, required to support the clinical research, maintained and stored on the EHR rather than duplicating it in the sponsor's database (e.g., medical history, prior medication and procedures). Data necessary to prove efficacy and safety would still exist within the sponsor's submission datasets as well as the EHR.
- Potential investigator list is expanded to include any physician with a certified EHR/CR system

5.6 Potential EHR/CR Roles and Responsibilities

This section provides discussion on clinical research roles and responsibilities that may evolve with the onset of national electronic health record systems capable of use for clinical research data collection. It

is provided to prompt additional discussion and thinking with regard to the nature of clinical research in the future.

1. Roles & responsibilities in all areas will evolve:
   - Clinical Research Associate (CRA): The traditional work of the CRA will migrate into more of a site relationship management role. The EHR/CR system removes the need for much of the CRA's time to be spent checking and managing paper CRFs allowing time on-site to be spent more effectively providing protocol and safety training, ensuring GCP compliance, etc. The EHR/CR software gives the CRA access to the patient data when not at the site, allowing for more targeted preparation of visits. The need for source data verification will largely be replaced by verification that the data points extracted to the eCRF are the correct data points. More complex interrogation of the EHR may allow the detection of omitted information such as non compliance with exclusion criteria, non-reporting of prohibited concomitant medications, etc.
   - Data Manager: This role changes to be far more site oriented, as data managers become the liaison between the data and the site staff communicating primarily via the EHR/CR system. Preparation of ongoing reports for safety and review purposes and programming of extraction algorithms may move this toward a more technical role. New tasks might involve transferring research data back to EHR (e.g., laboratory data). In addition, Data Managers will have more involvement in protocol development as data definitions will need to be built into the protocol to assist ethics committees/IRBs in reviewing data collection requirements and to enable the development trial-specific EHR modules.
   - Information Technology (IT) Support Personnel: IT staff will need to be more aware of the total process of clinical trials from eSource through submissions. They will need to be more involved in defining the study protocol, as it will additionally need to specify electronic methods of data collection and identify electronic source.
   - Quality Assurance: QA must audit EHR/CR systems to ensure appropriate controls exist such that investigators can be accountable for the integrity of the data (eSource) they provide. This will be facilitated by a robust EHR certification process.

2. The informed consent process will change. This will include all that are involved in the process (e.g., sponsor, site, patients and IRB/ethics committees):
   - Data is moving to patient ownership. The informed consent documentation will need to be adapted to collect patient approval for clinical trial participation
   - Informed consent can be given electronically

3. Some cost may be shifted due to a shift in some responsibilities for activities such as data hosting, on-site validation (data/system), trial module development/configuration

4. Review of data for fraud will change:
   - Fraudulent data will likely be reduced (never eliminated) as sponsors will be able to monitor the timeliness of the data entry and any changes
   - Since the EHR is usually accessible to many medical and nursing staff, it is less vulnerable to fraudulent changes by an individual
   - The sponsor will look for data trends, in order to detect fraud

6 CRITICAL SUCCESS FACTORS AND RISKS

6.1 Critical Success Factors for an EHR/CR System

While we recognize the magnitude and priority of the national eHealth initiatives to implement national health networks that will drive the cost of healthcare down while bringing up healthcare quality, we feel strongly that the earlier in this process the needs of clinical research are considered, the better for the entire healthcare community. Encouraging the growth of EHR systems without consideration of the regulatory requirements and efficiency needs of clinical research could bring unwanted consequences to the healthcare industry and to patients themselves, as a result of reduced efficiencies in the clinical research process, which could further result in an overall decline in the rate of introduction of new therapies and an increase in their costs.

The next evolutionary step for EDC in clinical trials is eSource and the elimination of duplicate record keeping. This is paralleling the national eHealth initiative efforts to move all clinical practices toward electronic data for all patient health records. In order for these electronic health records to be used for clinical research purposes there are some critical issues that must be addressed. The time is right for discussing these issues. Capturing patient data so that it can be used for both healthcare and research purposes can only be accomplished through the use of common data standards, and common regulatory guidelines for privacy, security, and record integrity. Collaboration between the healthcare industry and the bio-pharmaceutical industry is critical for influencing the goals of the eHealth initiatives, communicating with the stakeholders, and determining the details of the records, systems, networks, and processes. Not only can the data be captured in such a way as to facilitate both needs, but a strategic alliance between the two industries can be made -- thus facilitating ongoing communication and collaboration toward timely research of critical healthcare needs as they arise.

The following defines what we believe are critical success factors for accomplishing this vision and will position both healthcare and clinical research for success:

- Convince governmental decision makers that there is value in incorporating the facilitation of prospective clinical research as a goal of the National Electronic Health Initiatives
- Collaboration between the bio-pharmaceutical and healthcare industries and associated vendors to expand and adapt the structure of EHR and the associated systems, networks, and processes
- Development and testing of a standards-based use case that incorporates clinical research data collection in conjunction with national initiatives such as IHE (Integrating the Healthcare Enterprise) or AHIC (American Health Information Community)
- Develop certification specifications for EHR/CR systems to be included with national EHRS certification requirements
- Continue advocating for appropriate exemptions from anti-kickback laws and regulations (e.g. US Stark legislation (35) that prevent manufacturers from providing financial support for eHealth systems and networks.) Without appropriate safe harbors, it may be difficult for the bio-pharmaceutical industry to provide tools that can be used. A possibility is for the bio-pharmaceutical industry to sponsor work on EHR models and certification and national infrastructures rather than supporting technology in individual physician practices.
- Investigate the use of payer-based health records as a source of data for clinical trials.
- Collaboration on common data standards (including EHR narratives) and data transfer standards to support both national health record and clinical research needs (e.g., support for the CDISC/HL7 joint initiative)
- Modification of regulatory guidelines to support the use of eSource

- Modification to data privacy laws to enable clinical research while maintaining patient anonymity (e.g., HIPAA, EU Data Protection Directive)
- Application of 21 CFR Part 11 Electronic Records and Signatures Rule to EHR systems, or adaptation thereof
- Security technology for electronic transfers and transactions (e.g., 21 CFR Part 11, and SAFE)

6.2 Concerns with Current eHealth Plans Toward Meeting the EHR/CR Vision

The priority for implementing national health information networks has been driven by the ever increasing costs of healthcare and associated services. While the requirements of the bio-pharmaceutical industry have a lower priority, accounting for these needs now is critical to the future advancement of quality and cost effective clinical research. This will enable clinical researchers to identify, attract and manage patients and patient data, and speed delivery of breakthrough medicines, therapies and devices.

If clinical research is not incorporated into EHR system plans now, there is the potential for difficulty in recruiting investigators as the use of electronic patient records increases. The additional workload of clinical research data collection on top of the already-imposed requirement to collect healthcare data electronically makes clinical research economically impractical especially in the current cost-containment climate in the healthcare industry. Without an EHR/CR, there is the concern that the only source of data could be EHR systems that are not suitable for clinical research and which do not meet clinical data regulations unless the data is redundantly recorded in a regulatory-compliant method (either paper or electronic). Thus, without a suitable means to collect clinical research quality data within the EHR, clinical research will become more inconvenient and more expensive due to a redundant and less efficient process.

If clinical research becomes economically prohibitive due to the cost of running clinical trials coupled with the already crippling effects felt through the introduction of generic drugs and current patent laws, the impact to national health and to individual patients could be immense. This could very well inhibit the discovery of breakthrough drugs or research on diseases affecting small populations. While dealing more effectively with routine healthcare issues and improving the ability of a nation to identify an emergent healthcare crisis through a nationwide network of electronic health records, the ability of the research community to quickly conduct research and development to combat an emergency such as a new or evolved disease strain could be hampered.

In countries where eHealth initiatives have gone past the design phase and into implementation, the lack of common EHR data standards, code sets, and vocabularies, within and across countries, may make it difficult if not impossible to access and integrate this data efficiently for clinical research.
While electronic health records may come under existing federal regulations (e.g., HIPAA, Federal Rule of Evidence, EU Data Protection Directive) to ensure their security and integrity, these may fall short of what is needed for clinical research, and so it is critical to harmonize these regulations with those that apply to clinical research (e.g., 21 CFR Part 11, 21 CFR 312).

A further concern is that EHR system vendors and service providers do not have economic incentive and lack the knowledge of clinical data workflow to build EDC-like capabilities (see section 3.2) into their products. There are efforts being made to address this and to better define the value and cost associated with incorporating clinical research needs within EHR systems (16). It is critical that clinical research professionals be included in the design and implementation phases of EHR such that the result is an EHR/CR.

7 STEPS TOWARD IMPLEMENTING THE VISION

It is not possible to develop and implement EHR/CR technology with its full potential at this time. However, by collaboration of members from the bio-pharmaceutical and healthcare industries, regulators, and vendors of EHR and EDC systems toward this common EHR/CR vision, a smooth evolution toward this state as an acceptable reality is possible. Following are steps in this direction that could be taken now.

7.1 Technology Industry

Collaboration between EDC and EHR system vendors needs to occur for either one to compete in the market for clinical research money. Both have knowledge, software, processes, and services that need to be combined in order for the EHR/CR vision to become an acceptable and beneficial reality for all stakeholders. A new business model for these industries, targeted at a combined EHR/CR, needs to be developed. While interim steps may include multiple bridges and interfaces to existing applications, only an integrated solution will ultimately be beneficial and successful.

It is recommended that both EHR and EDC vendors:

- Work together with members from the bio-pharmaceutical and healthcare industries, regulators and other government agencies toward a common vision for EHR/CR.
- Work toward integrating the "parallel universe" of clinical research and physician health records when designing/upgrading their products
- Continue to support CDISC/HL-7 standards:
  - Integrate these standards when designing or upgrading EHR and EDC products
  - Add support for import and export using these standards
- Incorporate features into existing products to allow the secure use of eSource in today's environment
- Incorporate into applications the ability for secure, encrypted data to be passed over the internet
- Incorporate into applications (as an interim step), the potential to use EDC to load data from an EHR, central labs, or other third parties
- Continue to support the SAFE(18) initiative

7.2 Bio-pharmaceutical Industry

The bio-pharmaceutical industry cannot just sit back and wait to see what happens with the eHealth initiatives and the onset of more and more healthcare data being collected via eSource. It must be proactive in ensuring its ability to attract and keep investigators, that the investigators will continue to collect quality research data, and that the process of developing new drugs and bringing them to market continues to be cost-effective.

It is recommended that the bio-pharmaceutical industry:

- Work together with vendors of EHR and EDC systems, healthcare industry, regulators, and other government agencies toward a common vision for EHR/CR
- Continue to support the joint work of the CDISC/HL-7 committee
  - Request clinical data transfers using CDISC standards
  - Use CDISC standards in internally developed applications
- Maximize the number of studies conducted with EDC in order to prepare all clinical data management and investigator staff for an electronic environment

- Audit investigators who are already using EMR/EHR to determine the level of ALCOA associated with their patient data and make recommendations on improving these data such that they might be used as eSource for clinical trials
- Discuss with their investigators the need for requesting clinical research capabilities in their EMR systems and urge investigators who are considering purchasing/implementing EHR systems to consider systems that provide for a secure method for eSource collection and other clinical research data capture functionality
- Plan for changing business processes surrounding clinical trial data collection and management to accommodate EHR/CR vision
- Continues involvement and feedback of eSource pilot projects
- Work with regulatory agencies to be sure that regulations can support whatever model is being designed for eSource
- Find ways to sponsor eHealth initiatives such that the certifiable EHR systems will have hooks for clinical research

7.3 Government Agencies

Government agencies dealing with either national healthcare or bio-pharmaceutical drug control need to realize that the health of the overall population is best served through supporting a national electronic healthcare network that includes clinical research.

In addition to recommendation in Section 6.1, it is recommended that government agencies:

- Work together with members from the bio-pharmaceutical and healthcare industries and vendors of EHR and EDC systems toward a common vision for EHR/CR
- Allow use-cases for the national network to include functionality needed for clinical trial data capture (i.e. as a clinical trials use-case or part of a bio-surveillance use-case)
- Work together across regulatory agencies to ensure that common and/or complimentary regulations are applied to EHRs and clinical research data collection.
- Provide guidance on using electronic data as source for clinical trials
- Collaborate with both healthcare and bio-pharmaceutical industry groups when setting EHR technical and record content standards such that clinical research needs and regulations are met (i.e. endorse joint CDISC/HL-7 standards for EHR systems)
- Determine how to uniquely identify all individuals who may use a national health network
- Continue work on developing a certification process for EHR systems to determine adherence to approved standards for architecture, record content and validation
- Provide incentives for healthcare provider associations (both government sponsored and private sector) to follow set EHR standards and employ EHR systems
- Modify privacy regulations in order to provide for informed consent at different levels such that it can accommodate needs of access to patient data for both clinical trials research and data mining

7.4 Healthcare Providers

In most developed countries, initiatives for national electronic healthcare systems are under development and healthcare providers will be required to collect and maintain patient health records via an electronic record system. This will require a change in the way healthcare data is recorded, handled, and stored and can affect the processes in all areas of patient care.

It is recommended that members of the healthcare industry:

- Work together with members from the bio-pharmaceutical industry, regulators, and vendors of EHR and EDC systems toward a common vision for EHR/CR

- Start planning now for moving to an electronic environment.
- If not currently participating in any EDC clinical studies, request to run a trial using EDC. EDC is a good transitional environment for getting accustomed to electronic record keeping. This could be particularly beneficial to those organizations that are planning on moving to an EHR system. The training in processes and systems along with the ongoing support from EDC professionals provided by the sponsor will be invaluable in adjusting to an electronic records environment
- When researching EHR systems for purchase/implementation, talk to vendors about products that enable capturing electronic health records along with clinical research data

8 CONCLUSION

Clinical research requirements must be included in current plans for nationwide eHealth initiatives in order to achieve cost-effective and timely new therapies.

In the current environment where approximately 27% of clinical research is conducted using electronic data capture (EDC), a significant number of these investigative sites are also using electronic patient records systems. Although this duplicative environment may result in inconvenient and costly procedures for both healthcare and clinical research, it will be necessary during this transitional period of time and will enable them to leverage their EDC experience to quickly come up to speed in the EHR environment. However, as the use of EHR systems grows, the number of sites with these inefficiencies will grow to encompass all studies and all sites. This in turn will drive up the cost of clinical research immensely and could result in difficulty in recruiting investigators due to the added workload. This is especially significant during a time when the cost-containment climate in the healthcare industry is resulting in pressure on the bio-pharmaceutical industry to also contain costs.

Bio-pharmaceutical Industry and all medical researchers need to find a voice (and take action!) in the National eHealth Initiative debate.

Healthcare and research automation efforts are for the time being sector-centric. We need to collaborate and integrate if we are to improve the efficiency of data collection, minimize the effort from healthcare professionals in conducting clinical research, exchange reliable data, and ensure that regulatory approval of future therapies is based upon reliable and secure data sources. To achieve this, the bio-pharmaceutical industry and all medical researchers need to find a voice and take action in the EHR/ Healthcare Technology debate.

9 REFERENCES

9.1 Documents Referenced in this Document

1. Rand Corporation. Widespread Adoption Of Health Information Technology Could Save $162 Billion A Year, Says RAND Study, But The Federal Government Needs To Help. (As reported by CNN, 14-Sept-05). http://healthaffairs.org/press/septoct0501.htm

2. Harris Interactive, Aug 8, 2002. http://www.harrisinteractive.com/harris_poll/

3. Europe's Information Society Thematic Portal : http://europa.eu.int/information_society/activities/health/policy_action_plan/working_group/index_en.htm#Member%20States

4. Bio-IT World 'E-Source is Coming', report of CDISC 2004 survey, July 2005. This figure includes the use of ePRO trials.

5. Linda T. Kohn, Janet M. Corrigan, and Molla S. Donaldson, Editors; Committee on Quality of Healthcare in America, Institute of Medicine. To Err Is Human: Building a Safer Health System, 2000

6. Jan Walker, Eric Pan, Douglas Johnston, Julia Adler-Milstein, David W. Bates, and Blackford Middleton. The Value of Healthcare Information Exchange and Interoperability. January 19, 2005. http://content.healthaffairs.org/cgi/content/full/hlthaff.w5.10/DC1

7. EU Action Plan for Health: Action Plan for the European eHealth Area, 2004 http://europa.eu.int/information_society/doc/qualif/health/COM_2004_0356_F_EN_ACTE.pdf

8. Medical Group Management Association Center for Research and the University of Minnesota. Adoption of Electronic Health Records, 2005. http://www.mgma.com/research/index.cfm

9. Open Clinical Global EMR Deployment. EMR national deployment strategies and programmes http://www.openclinical.org/emrDeployment.html

10. Bio-IT World, EDC at JNJ, Part I: A Sponsor Ahead of the Cutting Edge**,** Oct. 5, 2005. http://www.bio-itworld.com/archive/eclinica/index_10052005.html

11. US, FDA. 21 CFR 312.62(b) Investigational New Drug Application: Investigator recordkeeping and record retention, latest amendment March 4, 2002. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62

12. U.S. FDA,. Guidance for Industry, Part 11, Electronic Records; Electronic Signatures - Scope and Application, August 2003. http://www.fda.gov/cder/guidance/5667fnl.htm

13. U.S. FDA. Guidance for Industry-Computerized Systems Used in Clinical Trials, April 1999. http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm

14. U.S. Dept of Health and Human Services. 45 CFR Part 46, Title 45 Public Welfare, Part 46 Protection of Human Subjects, June 23, 2005 http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

15. U.S. FDA. 45 CFR Parts 160 and 164. HIPAA: Health Insurance Portability and Accountability Act (1996) including the Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule; compliance date April 14, 2004). http://www.hipaadvisory.com/regs/finalprivacy/

16. FDAnews Drug Daily Bulletin. 01/13/2006, "Experts: Drugmakers Likely to Foot Bill in Combining of EHR and EDC"

17. Institute of Medicine, "Crossing the Quality Chasm: A New Health System for the 21st Century (2001)"

18. The Secure Access for Everyone (SAFE) initiative. http://www.safe-biopharma.org/

19. CDISC. Leveraging the CDISC Standards to Facilitate the use of Electronic Source Data within Clinical Trials. http://www.cdisc.org/publications/index.html

20. PhRMA EDC Task Group, Position Paper on Electronic Data Capture-Revision 1, May, 2005

21. ICH (International Conference on Harmonisation), FDA, E6 Good Clinical Practice: Consolidated Guidance", p. 21, 1996. http://www.fda.gov/cder/guidance/959fnl.pdf

22. Kenneth A. Getz, Applied Clinical Trials, The Imperative to Support Site Adoption of EDC. Jan 1, 2006. http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=283027

23. FDA, Guidance for Industry: Patient Reported Outcomes Measures: Use in Medical Product Development to Support Labeling Claims, *Draft*, February 2006. http://www.fda.gov/cder/guidance/5460dft.pdf

24. Siemens Medical Systems in conjunction with the Technical University of Munich (as presented at the eClinical Forum meeting in Bethesda, US), September 2005

25. Liora Alschuler, Landen Bain, Rebecca Kush, Meredith Nahm and Roberto Ruggieri, "Traditional Remedies for Clinical Trials and Healthcare Information," December 2003. Information on this pilot is at www.cdisc.org. Technology providers: Microsoft, Topsail Technologies, Digital Infuzion and Sentillion. Industry support: Merck & Co., Inc., Johnson & Johnson PRD, Novartis, Microsoft, Duke Clinical Research Institute and CDISC.

26. Mike Bartlett, Lundbeck Pharmaceuticals, "eSource - Review and Recommendations for Best Practice: The Sponsor's view" presentation to the eClinical Forum meeting, June 2004, and "Sponsor Hosting of eSource for eCRFs", presentation to DIA meeting "Four Worlds – One Vision", November 2005

27. PhRMA IMPACC Information Management Policy Affairs Coordination Committee, "Role of the Biopharmaceutical Industry in the Growth and Adoption of HIT in the US Healthcare System, April 29, 2005.

28. Karolinska Institute in Stockholm, Sweden (as reported by Dr Krister Kristianson of the Karolinska Institute to the Oct. 2005 eClinical Forum meeting in Edinburgh, Scotland)

29. US Department of Health and Human Services, Centers for Medicare and Medicaid Services, MEDICARE "PAY FOR PERFORMANCE (P4P)" INITIATIVES, January 31,2005 http://www.cms.hhs.gov/apps/media/press/release.asp?Counter=1343

30. American Geriatrics Society, Pay for Performance (P4P) Primer, 2006. http://www.americangeriatrics.org/policy/2006p4p_primer.shtml#8

31. American College of Physicians, Reform of the Dysfunctional Healthcare Payment and Delivery System, Position Paper, 2006.

32. Kristin Eilenberg, Amy Hoover, Michael Rutherford, Catherine Melfi, and Scott Segal, From Informed Consent through Database Lock: An Interactive Clinical Trial Conducted Using the Internet, Drug Information Journal, Vol. 38, pg 239 – 251, 2004.

33. Medical Records Institute, 6th Annual Survey of Electronic Health Record Trends and Usage for 2004, http://www.medrecinst.com/pages/latestNews.asp?id=115

34. Garets, Dave and Davis, Mike, Electronic Medical Records vs. Electronic Health Records: Yes, There is a Difference, HIMSS Analytics, LLC, January 26, 2006.

35. National Alliance for Health Information Technology, Letter to US Dept of Health and Human Services "Proposed Regulation at 42 CFR Part 411", Dec 8, 2005.

9.2 Websites

The following websites may be instrumental in getting information on current initiatives that could further benefit or affect this vision:

9.2.1 Standards Initiatives

- Health Level 7 (HL7): http://www.hl7.ca
- Clinical Data Interchange Standards Consortium (CDISC): http://www.cdisc.org
- Joint CDISC / HL7 Charter: http://www.cdisc.org/single_source/about.html
- Biomedical Research Integrated Domain Group (BRIDG): http://www.bridgproject.org/
- Healthcare Information Technology Standards Panel (HITSP): http://www.ansi.org/standards_activities/standards_boards_panels/hisb/hitsp.aspx?menuid=3http://www.ansi.org/
- openEHR Foundation: http://www.openehr.org/
- Certification Commission for Healthcare Information Technology (CCHIT): http://www.cchit.org
- Integrating the Healthcare Enterprise (IHE): http://www.himss.org/content/files/infosheets/Integrating_the_Healthcare_Enterprise.pdf http://www.ihe.net/Technical_Framework/upload/ihe_tf_rev6.0ft_vol4_2005-04-15.pdf http://www.ihe.net/
- Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT): http://www.snomed.org
- MedDRA: http://www.meddramsso.com
- Laboratory Logical Observation Identifier Name Codes (LOINC): http://www.loinc.org
- Consolidated Health Informatics (CHI): http://www.hhs.gov/healthit/chi.html
- The Secure Access for Everyone (SAFE) initiative: http://www.safe-biopharma.org

9.2.2 National and Community eHealth Initiatives

- Open Clinical: EMR National Deployment Strategies and Programmes (links from this site to sites of national eHealth initiatives): http://www.openclinical.org/emrDeployment.html

- US Health & Human Services (HHS), Office for the National Coordination for Health Information Technology (ONCHIT) : http://www.hhs.gov/healthit
- Integrating the Healthcare Enterprise (in the US) (IHE): http://www.ihe.net/
- eEurope e-Health initiative (EU): http://europa.eu.int/information_society/eeurope/2005/all_about/ehealth/index_en.htm#European%20Challenges
- Action Plan for the European eHealth Area: http://europa.eu.int/information_society/doc/qualif/health/COM_2004_0356_F_EN_ACTE.pdf
- Regional Secure Healthcare Networks (RESHEN): http://www.biomed.ntua.gr/reshen/
- European Institute for Health Records (Eurorec): http://www.eurorec.org/
- WideNet: http://www.sadiel.es/Europa/widenet/acceso.htm
- NPfIT (UK National Programme for IT): http://www.npfit.nhs.uk
- Danish Center for Health Telematics: http://cfstuk.temp.fyns-amt.dk/default.asp?id=150961
- National Cancer Institute (NCI) Cancer Biomedical Informatics Grid (caBIG)

9.3 Glossary of Terms

Term	Description
ALCOA	According to the CSUCT Guidance (13), "to be acceptable the data should meet certain fundamental elements of quality whether collected or recorded electronically or on paper. Data should be attributable, original, accurate, contemporaneous, and legible." This principle is referred to in the industry as ALCOA.
CDMS	Clinical Data Management System (clinical trial sponsor's database used to collect and maintain clinical research data)
Clinical Trial	Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one of more investigational medicinal product(s), and /or to identify any adverse reactions to one or more investigational medicinal product(s), and/or to study absorption, distribution, metabolism and excretion of one of more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy. [Directive 2001/20/EC; Modified from ICH E6 Glossary]
CRA	Clinical Research Associate (a member of the clinical trial sponsor's staff who monitors the progress of investigator sites participating in a clinical trial)
CRF, eCRF	Case Report Form (form used to present clinical research data) Electronic Case Report Form
CRO	Contract Research Organization (provides services to the bio-pharmaceutical industry for assistance in running clinical trials)
EDC	Electronic Data Capture of clinical research data via systems that provide electronic support for data capture and management at the investigator site and communication between the site and the sponsor
eDiary, ePRO	Electronic Patient Reported Outcomes - Patient-entered experience data that is entered into an electronic device often referred to as eDiary or ePRO device
eHealth	Government initiatives focused on developing nationwide electronic health networks
EHR/CR	Term coined in this paper. Refers to a system that is capable of supporting both

	electronic healthcare and electronic clinical research data capture.
EHR	A subset of each care delivery organization's EMR, is owned by the patient and has patient input and access that spans episodes of care across multiple care delivery organizations within a community, region, or state (or in some countries, the entire country) (34). The EHR is expected to ride on a national health information network.
EMR	An application environment composed of the clinical data repository, clinical decision support, controlled medical vocabulary, order entry, computerized provider order entry, pharmacy, and clinical documentation applications. This environment supports the patient's electronic medical record across inpatient and outpatient environments, and is used by healthcare practitioners to document, monitor, and manage healthcare delivery within a care delivery organization (CDO). The data in the EMR is the legal record of what happened to the patient during their encounter at the CDO and is owned by the CDO. (34)
eSource	"When original observations are entered directly into a computerized system, the electronic record is the source document." FDA Guidance on Computerized Systems Used in Clinical Trials section III.D (note: also commonly referred to as "direct entry")
GCP	Good Clinical Practice: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. NOTE: For Guidance on Good Clinical Practice see COMP/ICH/135/95; Declaration of Helsinki; 21 CFR 50, 21 CFR 54, 21 CFR 56, and 21 CFR 312. [ICH]
FDA	United States Food and Drug Administration
HIT	Health Information Technology
Hosting	In this paper, hosting means providing the computer facilities (servers) and procedures for a safe custody/storage of clinical data in such a way that data are protected against un-authorized access during and after a trial. The host is responsible for ensuring the ALCOA-principle.
ICH	International Conference on Harmonization (Provides regulatory guidelines for clinical trials)
NHS	National Health Service (United Kingdom)
SAFE	The Secure Access for Everyone (SAFE) initiative, supported by group of major bio-pharmaceutical companies in cooperation with regulators and industry associations, is a collaborative effort to create an industry-wide e-signature standard. SAFE's mission is to provide an open global standard for secure and legally enforceable digitally signed e-documents exchanged among bio-pharmaceutical companies and with regulatory bodies.
SDO	Standards Development Organization
Source Data	ICH GCP Guideline E6: 'All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).'