

eSource Implementation in Clinical Research: A Data Management Perspective

A White Paper

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Table of Contents

Acknowledgments.....	2
1. Abstract	3
2. Introduction.....	3
Electronic Health Records in Clinical Care	3
Technology and Standardization in Clinical Research	5
Pace of Regulatory Guidance.....	6
3. eSource Principles of Use	8
Principle 1: Use solutions that are "fit for purpose"	8
Principle 2: Declare the source	9
Principle 3: Capture data when first generated	9
Principle 4: Control electronic data	10
Principle 5: Leverage automated quality checks.....	11
Principle 6: Control for quality	12
Principle 7: Conform to regulations and guidelines	13
4. Data Collection Modalities	14
Third-Party Generated Sources (Central Laboratories, ECG Data, IRT, etc.).....	15
Electronic Clinical Outcome Assessment (eCOA, eDiaries, ClinRO, ObsRO) to capture Patient-Reported Data	18
Sponsor/CRO Electronic Data Capture	22
Site Controlled EHRs.....	24
5. Future Directions	28
6. Conclusion	30

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1. Abstract

Electronic technologies have redefined industries such as banking and commerce. Similarly, advances in technology are bringing massive changes to the healthcare realm, nearing a tipping point for overhauling every aspect of healthcare delivery and records management. As the paper chart is inevitably displaced in the daily practice of healthcare, it follows that the paper case report form (CRF) and paper site source documents for clinical research will also be displaced, ushering in the era of electronic source (eSource) for clinical studies. This transformation presents both opportunity and challenge for data management as we approach the intersection of the delivery of care and clinical research.

To achieve the full potential of eSource in clinical research, the process for data collection must be transformed from the traditional paper CRF collection model and associated paper site source documents to one that optimizes the availability of electronic data records while ensuring that data integrity and patient safety are not compromised. True transformation will preserve the requisite standards of conduct while reinventing the data collection process and governing regulations to fit the new electronic environment. This transformation is sure to surface many challenges—some real and some simply perceived.

The Society for Clinical Data Management (SCDM) has identified constructive principles and best practices for different modalities organized by process, people and technology to address these challenges. We present various data collection modalities of eSource and relevant considerations for successful implementation.

2. Introduction

The earliest attempts of electronic health records (EHR) for clinical care significantly preceded the advent of dedicated electronic data capture (EDC) for clinical research, but both race toward jettisoning paper records and offering the clinician the opportunity to enter data only once and enable its multiple appropriate uses. As is often the case, regulation is informed by these early attempts and must foresee the transformed future and not merely an electronic version of the past.

Electronic Health Records in Clinical Care

The idea of recording patient information electronically instead of on paper—the Electronic Medical Record (EMR)—emerged in the late 1960s, when Larry Weed introduced the concept of the Problem Oriented Medical Record into medical practice.¹ Until then, doctors usually recorded only their diagnoses and treatment. Weed's innovation was to generate a record to allow a third party to independently verify the

¹Weed LL: Medical Records That Guide and Teach. N Engl J Med 278:593-600, 1968

diagnosis. In 1972, the Regenstreif Institute developed the first medical records system. Although the concept was widely hailed as a major advance in medical practice, physicians did not flock to the technology.²

In 1991, the Institute of Medicine, a highly respected think tank in the United States (US), recommended that by the year 2000 every physician should be using computers in their practice to improve patient care and made policy recommendations on how to achieve that goal.³

The adoption of eSource from EHRs for clinical research has been slow, in part because implementation of eSource from EHRs is complex. To improve uptake, questions must be answered about what programs should be contemplated and what checks can be implemented to ensure data integrity, protect patient privacy, create audit trails, restrict access appropriately, permit monitoring, and satisfy regulatory inspections.

Historically, clinicians recorded patient data onto paper patient charts and clinical research likewise leveraged paper case report forms. Regulatory inspectors are long accustomed to inspecting such paper records to verify the integrity of reported trial data. Clinicians are now replacing paper patient charts with electronic health records.

A 2012 survey of primary care physicians in 10 countries indicates 69% of US doctors are using EHRs compared to 98% primary care physician EHR use in the Netherlands, 98% in Norway, 97% in New Zealand, 97% in the UK, 92% in Austria, 82% in Germany, 67% in France, 56% in Canada and 41% in Switzerland.⁴ A 2010 study on EMR/EHR markets in the Asia Pacific region projected a 7.6 percent compound annual growth rate from \$2.3 billion in 2010 to \$2.9 billion in 2013, although other predictions suggest much more rapid growth in the region.⁵ The 2010 study also suggests emerging markets, such as Malaysia, Thailand, India and China could leapfrog other nations by learning from the experience of other nations and applying innovative approaches such as cloud-based solutions.

² Regenstrief Medical Record System (RMRS) [Internet]. Clinical Informatics Wiki created 27 July 2005. Dean F. Sittig, Ph.D. [updated 2011 Oct 13; cited 2014 Mar 12] [about 4 screens]. Available from: [http://clinfowiki.org/wiki/index.php/Regenstrief_Medical_Record_System_\(RMRS\)](http://clinfowiki.org/wiki/index.php/Regenstrief_Medical_Record_System_(RMRS))

³ Institute of Medicine Committee on Improving the Patient Record, Division of Health Care Services, Editors: Richard S. Dick, Elaine B. Steen and Don E. Detmer. National Academy Press, Washington, DC, 1997. *The Computer-Based Patient Record: An Essential Technology for Health Care*, Revised Edition.

⁴ C. Schoen, R. Osborn, D. Squires, M. M. Doty, P. Rasmussen, R. Pierson, and S. Applebaum. A Survey of Primary Care Doctors in Ten Countries Shows Progress in Use of Health Information Technology, Less in Other Areas. *Health Affairs* [published online before print 2012 Nov 15; cited 2013 Feb 15] [about 19 screens] Available from: <http://content.healthaffairs.org/content/31/12/2805.full?keytype=ref&siteid=healthaff&ikey=Wx1r2YCsnJVL>.

⁵ Overview of International EMR/HER Markets, results from a Survey of Leading Health Care Companies. Accenture, [August 2010; cited 2013 Sep 2] [16 pages] Available from: http://www.accenture.com/SiteCollectionDocuments/PDF/Accenture_EMR_Markets_Whitepaper_vfinal.pdf.

The future of EHR in all these nations largely depends on regulatory standards and government support. Thus, clinical research sponsors must know how regulators will judge the acceptance of a site's EHR as a source record as the pool of investigators using paper records shrinks.

Technology and Standardization in Clinical Research

Electronic data capture (EDC) technologies began in the mid-1980s, reaching a tipping point in 2007⁶. Despite the tangible benefits of electronic data capture, the adoption of EDC systems has remained slow in some segments of clinical research. At the end of 2012, only 40% of Phase I clinical trials had adopted EDC⁷.

Likewise, Interactive Response Technology (IRT) has proven to be a major force driving innovations in biopharmaceutical research and development because it holds two sets of data vital to the success of a clinical trial: (1) patient information and (2) drug or device supply management information. Its transactional nature is one of the main reasons the technology has seen an increase in adoption. For example, as patients are recruited, the IRT assigns kit numbers and sends drug or device supplies directly to sites. Sites and sponsors/CROs monitor their drug or device inventory via the IRT and react by resupplying or returning supplies based on a number of factors. IRT technology is especially transactional in adaptive trials where changes in treatment arms, drug assignments, and dosage levels are administered by IRT systems in an automated manner.⁸

Electronic Clinical Outcome Assessment (eCOA) has also upped the ante by streamlining patient data collection using modern tools that bypass traditional printed forms. Although less than a decade ago most people accessed the Internet from a desktop computer, today many access it from mobile devices and tablets, making the availability and cost effectiveness of user-friendly Internet-enabled technologies more accessible. Such technologies have the potential to improve data quality by increasing the patient's access and convenience to the collection instrument so their assessment and data entry can be easily accomplished at the prescribed time rather than postponed to a time when their recollection and reporting may be less accurate.

⁶ Connor, Chris. April 2007. Health Industry Insights (an IDC company). Doc #HI206351. U.S. Electronic Data Capture 2006–2011 Spending Forecast and Analysis. See BusinessWire, Electronic Data Capture (EDC) Poised to Disrupt Life Sciences Industry, Say Health Industry Insights. [Internet] [created 2007 May 7; cited 2014 Mar 12] <http://www.businesswire.com/news/home/20070507005691/en/Electronic-Data-Capture-EDC-Poised-Disrupt-Life#.UyDGGvldW89>.

⁷ Challenges and Benefits of EDC Adoption [Internet]. Clinovo, [Created 2013 Apr 26; cited 2014 Mar 12] [about 9 screens]. Available from: <http://www.clinovo.com/blog/challenges-and-benefits-of-edc-adoption/>.

⁸ Bedford, Ph.D., Joseph. Almac Clinical Technologies. The Renaissance in IVR/IWR Systems Use of Interactive Response Technologies is on the Rise. [Internet] [cited 12 Mar 2014] Available from: www.almacgroup.com/wp-content/uploads/IVRIWR-Systems1.pdf.

As the technologies of EDC, IRT, eCOA and other electronic data capture opportunities gained traction, the ideal of standardization also gained supporters. The potential for sharing data, collaboration, and streamlining processes through the use of electronic data could be achieved if data were standardized in such a way as to support its collection and dissemination. Thus was born the Clinical Data Interchange Standards Consortium's (CDISC) eSource Data Interchange document (eSDI), written with the purpose "to investigate the use of electronic technology in the context of existing regulations for the collection of eSource data (including that from eCOA/ePRO, EHR, EDC) in clinical trials for regulatory submissions by leveraging the power of the CDISC standards, in particular the Operational Data Model (ODM)."⁹

Pace of Regulatory Guidance

The US Food and Drug Administration (FDA) enacted the 21 CFR Part 11 Electronic Records; Electronic Signatures regulation in 1997. The European Union (EU) adopted their electronic signatures Directive in 2001. In the years since, both measures have been evaluated and their regulatory/legal interpretation matured.

As noted by the Clinical Data Interchange Standards Consortium,

"...if a very strict interpretation of the regulations is taken, it could be argued that some solutions may not meet all of the current regulatory requirements. However, in a time of transition, there is a need to reflect upon the spirit of the regulations (and to keep in mind that some of these regulations were created for paper based documentation only) rather than using a literal interpretation. This view is necessary to adapt to the current environment and thus gain the benefit of new technology, while maintaining the necessary measures to ensure that clinical trial data continues to be of the highest quality and integrity."¹⁰

To address the more current adoption of technology, in 2010 the European Medicines Agency (EMA) released a Reflection paper on Expectations for Electronic Source Data and Data Transcribed to Electronic Data Capture Tools in Clinical Trials¹¹ and in 2011 a

⁹ Clinical Data Interchange Standards Consortium, Electronic Source Data Interchange Group. Leveraging the CDISC Standards to Facilitate the use of Electronic Source Data within Clinical Trials. [2006 Nov 20; cited 2013 Sep 2]. Available from:

<http://www.cdisc.org/stuff/contentmgr/files/0/2f6eca8f0df7caac5bbd4fadfd76d575/miscdocs/esdi.pdf>.

¹⁰ Clinical Data Interchange Standards Consortium, Electronic Source Data Interchange Group. Leveraging the CDISC Standards to Facilitate the use of Electronic Source Data within Clinical Trials. [2006 Nov 20; cited 2013 Sep 2]. Available from:

<http://www.cdisc.org/stuff/contentmgr/files/0/2f6eca8f0df7caac5bbd4fadfd76d575/miscdocs/esdi.pdf>.

¹¹ European Medicines Agency, 9 June 2010; EMA/INS/GCP/454280/2010; GCP Inspectors Working Group (GCP IWG). Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials. [2010 Jun 9; cited 2013 Sep 2] Available from:

draft Reflection paper on the Use of Interactive Response Technologies (Interactive Voice/Web Response Systems) in Clinical Trials¹². Per the 2010 Reflection paper,

“Collection of accurate clinical trial data is essential for compliance with Good Clinical Practice (CPMP/ICH/GCP/135/95)¹³. With increasing use of information technology in pharmaceutical development there is a need to have clear guidance on the use of electronic source data and transcribed data and the principles that should apply to them. This is necessary in order to ensure that the processes can be used and accepted with confidence when such requirements are complied with, and that the benefits that these systems offer can be fully utilized.”

The US FDA issued Guidance for Industry on Computerized Systems used in Clinical Investigations (CSUCI) in 1999¹⁴ and updated it in 2007.¹⁵ Per CSUCI,

“The computerized system applies to records in electronic form that are used to create, modify, maintain, archive, retrieve, or transmit clinical data required to be maintained, or submitted to the FDA. Because the source data are necessary for the reconstruction and evaluation of the study to determine the safety of food and color additives and safety and effectiveness of new human and animal drugs, and medical devices, this guidance is intended to assist in ensuring confidence in the reliability, quality, and integrity of electronic source data and source documentation (i.e., electronic records).”

The US FDA has also issued two guidance drafts: in January 2011 the Guidance for Industry on Electronic Source Documentation in Clinical Investigations¹⁶ and a revision draft in November 2012 entitled Guidance for Industry on Electronic Source Data in Clinical Investigations.¹⁷

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf.

¹² European Medicines Agency, 5 August 2011; EMA/INS/GCP/600788/2011; Compliance and Inspection. Reflection paper on the use of interactive response technologies (Interactive Voice/Web Response Systems) in Clinical Trials DRAFT. [5 Aug 2011; cited 2013 Sep 2] Available from:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110227.pdf.

¹³ Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Volume 3C Efficacy, Rules Governing Medicinal Products in the European Union.

¹⁴ FDA, US Department of Health and Human Services, Office of the Commissioner, April 1999, Guidance for Industry Computerized Systems Used in Clinical investigations.

¹⁵ FDA, US Department of Health and Human Services, Office of the Commissioner, May 2007, Guidance for Industry Computerized Systems Used in Clinical investigations. [2007 May; cited 2013 Sep 2] Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf>.

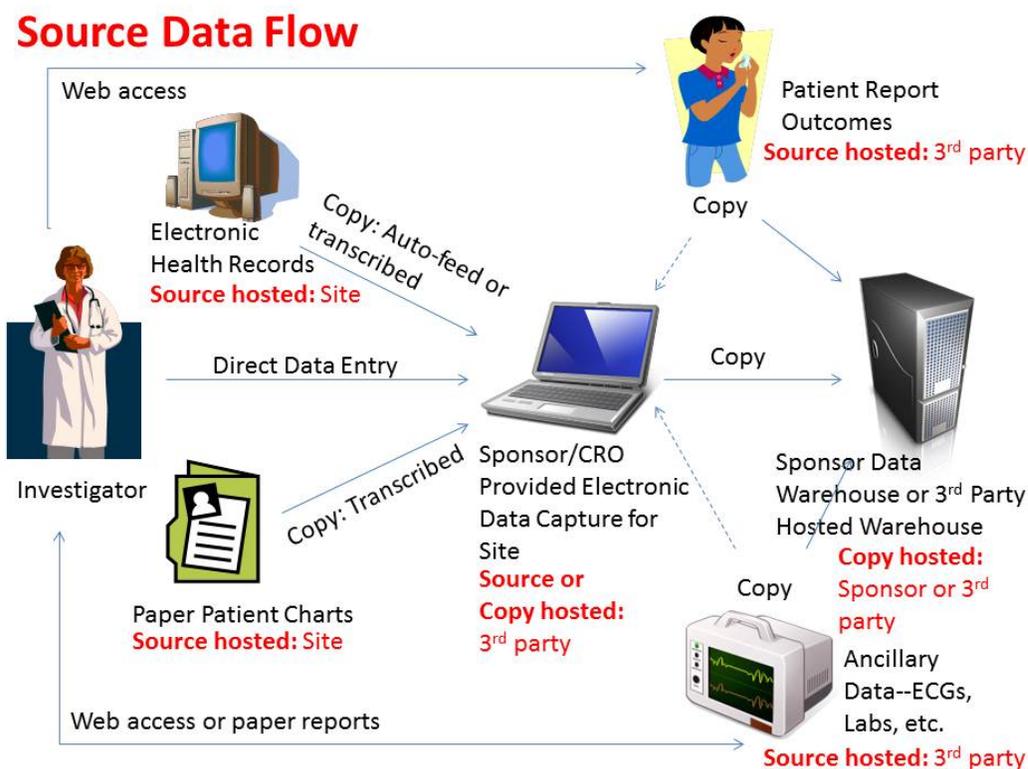
¹⁶ FDA, US Department of Health and Human Services, January 2011, Guidance for Industry Electronic Source Documentation in Clinical Investigations DRAFT GUIDANCE.

¹⁷ FDA, US Department of Health and Human Services, November 2012, Guidance for Industry Electronic Source Data in Clinical Investigations DRAFT GUIDANCE.

The aforementioned guidance documents are aimed at describing what is expected to ensure eSource is a reliable and trustworthy source. The regulations point toward the desire to realize the potential benefits of electronic source yet the practical application of it falters over the exact wording of the regulations. Implementation activities grind to a halt with spiraling analysis of the needed software features and debate over regulatory interpretation. The result is a delay in the timely, appropriate and compliant introduction of new technology, when, in fact, what is needed is to consider the “spirit” of the regulations authored for a world using traditional paper CRFs combined with the content from more recently drafted guidance documents for electronic source.

3. eSource Principles of Use

When electronic source is properly implemented, it offers many benefits not possible with paper source records. The following principles are intended to guide organizations in an optimal, efficient and compliant implementation of eSource as denoted in Figure 1.



Note: Dashed lines reflect alternate dataflows.

Figure 1: Source Dataflow

Principle 1: Use solutions that are "fit for purpose"

Any electronic solution for source documentation should align with the needs of the trial. The gamut of functionality of eSource solutions is broad. Factors to consider include the modality, improved accuracy/data quality, efficiency, type of study, patient population, location of study/hospital and cultural considerations, site sophistication, program

consistency, timeliness of entry, protocol adherence and timeliness of availability (e.g., safety monitoring). Systems that are robust may be “overkill” and not practical for some trials; others may be too basic to capture the necessary information. To avoid any technological pitfalls that would make the use of eSource obsolete, the capability of the eSource solution to export data into a format that will easily integrate into the electronic data capture solution must be understood. The choice of the solution should be confirmed by all internal sponsor stakeholders and key opinion leaders.

Principle 2: Declare the source

Data in a trial may be generated from a mix of paper sources and electronic sources. Per the CDISC glossary, source data is 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).¹⁸ All computerized systems and data sources that a sponsor mandates for all sites (e.g., eCOA/ePRO, EDC) should be identified in the protocol. To capture other patient data, sites may elect to use eSource or paper source or a combination. The sponsor-mandated source decision will be documented in a data management plan or its equivalent. Sites must consistently document and apply their chosen method of source documentation for all patients. A source data location list should be maintained as part of the investigator’s trial file. The investigator’s primary responsibility is to patient care and safety. It is critical that the chain of custody of data from all sources through the final analyses data sets is properly documented and consistently applied such as in a dataflow document. The FDA Guidance for Industry Electronic Source Data in Clinical Investigations¹⁹ emphasizes the role of data element identifiers including originator as key elements in documenting eSource.

Principle 3: Capture data when first generated

For the many benefits it provides over paper records that are later data entered into a computer system, clinical data should be captured electronically by study site personnel or by patients (when eDiaries are being used) at the point of data generation to help:

- avoid transcription (and inherent errors) from paper records
- enable timely data review by the principal investigator
- enable timely data review by sponsor safety reviewers

¹⁸ CDISC Clinical Research Glossary. Version 8.0 [Internet] [2009 Dec; cited 12 Mar 2014] [51 pages] Available from: http://www.cdisc.org/stuff/contentmgr/files/0/be650811feb46f381f0af41ca40ade2e/misc/cdisc_2009_glossary.pdf.

¹⁹ FDA, US Department of Health and Human Services, September 2013, Guidance for Industry Electronic Source Data in Clinical Investigations. Procedural. [2013 Sep; cited Sep 2013] Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf>.

- enable real-time data quality checking
- capture a more accurate and complete audit trail
- reduce the volume of records to be source data verified or reviewed

Some of these benefits are achieved merely by capturing the data electronically when it is first generated as long as the data capture system properly manages the electronic records. However, some benefits are enabled only if the source is integrated with the sponsor's/CRO's clinical system. The sponsor's/CRO's real time safety review is enabled only if the electronic source is tightly coupled to the sponsor's/CRO's EDC system as the most robust real-time data quality checking is often only programmed into the sponsor's/CRO's systems.

Data captured at point of care may require a change in workflow at the site. To promote adoption of eSource, this new workflow should be efficient for the site. Mobile data collection is ideal.

Principle 4: Control electronic data

In the world of paper records, it is easy to understand the physical control that an investigator has over the paper source records at their site. The records still require proper management to remain effectively controlled but only transcribed copies are sent to the sponsor/CRO and the original source records physically remain at the site under a combination of physical (e.g., locked file cabinets) and procedural (e.g., restricted distribution of keys) controls implemented by the investigator. However, a true validation of data equivalence end to end (source to sponsor/CRO analyses database) was never truly feasible in the paper world. It was also never truly possible to know if a paper document was destroyed because a remaining audit trail would not be guaranteed.

In the world of electronic records, it is possible to control the integrity of data seen or modified by many parties over the lifetime of the record or we would not have the e-commerce solutions that drive so much of the global economy today. However, appropriate control of electronic records requires a very thoughtful implementation of a system of controls working together, some procedural (e.g., segregation of duties, standard operating procedures), some physical (e.g., different server locations to establish redundancy) and some electronic (e.g., computer security rights and roles). It may take significant effort to validate and commensurate inspection activity to verify such control systems are operating as designed.

In the context of a sponsor/CRO EDC system, the system may be used purely for transcription/transfer from an investigator-controlled source (paper or electronic) or as the source itself, if the data are entered directly in the sponsor/CRO EDC. It is important to acknowledge that just as source may be a certified copy or a transcription this does not mean that every transcription is and should be treated as source as prescribed by predicate rules. Three principles must always be followed as it is the principal investigator's primary responsibility for patient care and safety. Any data in any form to be considered source data:

- (1) must never be under the control of the sponsor/CRO,

- (2) must always be accessible to the investigator, and
- (3) must be under the control of the investigator through the legally determined timeframe.

Only a clinical investigator or delegated site staff should perform modifications or corrections to eCRF data. Modifications or corrections must be traceable by data element identifiers reflecting date, time, originator and reason for change. Ideally the eCRFs are kept at the site in an independent way (i.e., independent of a sponsor or CRO-controlled system). A fully independent trusted third party may be an alternative, but the definition of “independent” has not crystallized yet.

The investigator should have not only access but also sole control of content of the eCRF. The site’s eSource should not be changed without the express consent of the investigator as well as traceability of any changes easily identifiable by inspectors. Sites should have access and control of eSource to know what they have sent to the sponsor. This can be accomplished via a trusted third-party information technology (IT) organization with no data management responsibilities. Decommissioning any EDC system should follow chain of custody methods to show traceable data from the hosted venue to sites. Decommissioning should follow investigator confirmation of archiving to assure that direct access by the investigator never lapses.

In legacy EDC environments, where software programs ran on the sponsor’s/CRO’s computers (thick client) located at a clinical investigation site and the data was stored on electronic media at the same site, the perception may have existed that the electronic records were under the investigator’s direct control. However, if such systems ever exchanged removable media, were linked directly to sponsor’s/CRO’s systems to transfer records or update software, or the sponsor/CRO provided the software or any administration of the system, then the effective control of those records depended on a validated system of controls.

The same state exists when computers and media are located away from the investigator’s premises—as so many Internet-enabled applications function today—except that the physical and procedure controls are often implemented by neutral IT third parties contracted to perform such duties. Whether such third party is contracted by the investigator or the sponsor/CRO should be immaterial if the system of controls is effective. Theoretically, the more parties engaged to perform independent roles in such a system of controls, the more clear segregation of duties likely exists, minimizing the ability of any one party to subvert the system of controls. While no shortcut for designing an effective system of controls exists, any techniques that implement greater segregation of duties should inspire more confidence in the effectiveness of the control system.

Principle 5: Leverage automated quality checks

Given that eSource is collected contemporaneously with the event without other documentation, the most effective way to ensure data integrity is to program front-end data verification checks (i.e., front-end validation checks) into the data capture system. Front-end edits allow the end user, patient or principal investigator, to verify the

accuracy or intent of the entry real time. Additionally, edit checks should look longitudinally across visits to ensure that consistent data are being captured. In the instances when the entry is an upload by a device or machine (e.g., blood pressure cuff), both the validation of the device/machine by the site and the validation of the transfer system by the site and sponsor/CRO is key to ensuring data integrity. In the legacy transcription world, verification checks post data submission are routine to check for transcription errors; however, in an eSource scenario, verification checks post eSource submission should be limited to checks across multiple sources, header data, etc. To be the most efficient, front-end validation checks should focus on key data elements that will be analyzed.

Principle 6: Control for quality

As part of the quality controls on data retrieved from eSource, system and user controls should be in place and appropriately documented to ensure all data collected from eSource meet ALCOA+CCEA (attributable, legible, contemporaneous, original, accurate plus complete, consistent, enduring, and available).

ALCOA+CCEA on eSource includes these elements:

- Data are captured in the eSource in such a way that they are **attributable**. The eSource system or device should capture information about who made the entry, or from what other electronic source it was derived. To facilitate a secure and auditable electronic system, security roles and user accounts should be created for each individual given access to the system. It is up to the sponsor and/or designated personnel to create and maintain these roles and accounts within the system and validate they function as intended. The investigational site should be properly trained and is responsible to ensure investigators and site employees use unique access to the EDC system and do not share user account information to avoid fraud or harm to any subjects. Sites should understand how the security controls work.
- Data are **legible** and in the appropriate language required by the local regulatory authorities, and, where applicable, conform to industry data format standards recognized and used by that regulatory authority, such as ODM, CDASH, CDISC Controlled Terminology, or SDTM.
- Data are **contemporaneous** so that it is known when the measurement or observation was made and when it was recorded in the eSource. If there was a time lag between the measurement and the time it was recorded in eSource, this should be recorded in the eSource with the data, or detectable from the audit trail. (See Principle 3: Capture data when first generated.)
- For the data to be considered eSource, they should be **originally recorded** or recorded as a certified copy in the system or device that is considered the source. If the eSource is another system, such as an electronic health record, or a device that captures data, adequate metadata to clearly identify the source should be transmitted along with the data. (See Principle 3: Capture data when first generated.)
- To ensure data are **accurate**, there should be known quality controls on the originating source, including validation of any processes, programs or systems

that transfer data from one source to another, acceptable calibration practices and documentation on devices that capture data automatically, operation of data capture devices by trained personnel, and procedures that describe these controls and the proper operation of the device.

- To ensure data are **complete**, a validated transfer process should be employed and additionally programmed edit checks can be automatically run to confirm that all data expected for mandatory data fields in a study have been retrieved from the electronic source. (See Principle 5: Leverage automated quality checks.)
- Programmed edit checks can also be employed to ensure **consistency** within and across data from various electronic sources. (See Principle 5: Leverage automated quality checks.)
- Process and technical controls should be in place to ensure that clinical records collected from an electronic source will **endure**; that is, that those records are maintained for as long as specified in applicable record retention requirements. Maintenance of such records should be accounted for in an organization's backup and recovery plans and procedures.
- Electronic records and their source should be maintained in such a way that they are **available** for review, and in a format that is suitable for review by a human for as long as the applicable record retentions requirements endure. This could be done by storing the records on enduring media (e.g., disc or tape) in a system-agnostic format (e.g., portable document format (PDF), extensible markup language (XML)).

Principle 7: Conform to regulations and guidelines

Understanding that regulatory bodies do not regulate various investigator eSource solutions used as part of source data collection in clinical trials, investigator eSource data capture systems should align with the spirit of US FDA 21 CFR Part 11 as much as possible. Sections of the regulation address the need for accurate, controlled recordkeeping of subjects' information in sponsor/CRO electronic data capture systems whether used as direct data entry systems (eSource) or holding transcribed data. Given these sponsor/CRO systems will rely on information contained in investigator eSource solutions, the same practices should be applied wherever possible. Sponsors/CROs need to define a process to determine the EHR's trustworthiness/access such as using the eClinical Forum's site checklist²⁰ for EHR reliability assessment that is under development.

²⁰ EHRCR (Electronic Health Records for Clinical Research) Project Team, eClinical Forum (www.ehrccr.org). June 2011. Release 1.0. Practical Considerations for Clinical Trial Sites using Electronic Health Records (EHRs) Certified for Clinical Research; Addressing Regulatory Considerations. Release 1.0. [Internet] [2011 Jun 1; cited 2014 Mar 12] [24 pages]. Available from: <http://eclinicalforum.org/ehrcrproject/en-us/documents.aspx>.

Like any paper-based system, investigators participating in clinical trials and using eSource for patient charting (e.g., EHRs) are expected to follow the retention requirements outlined in ICH E6 Section 8 and US FDA 21 CFR Part 314 and Part 312 regulations. Sites using eSource must understand the dataflow and how it meets the US FDA 21 CFR Part 312.62(b) obligations of maintaining case histories under this dataflow. Other guidance documents such as CDISC's eSDI, FDA's Guidance for Industry Electronic Source Data in Clinical Investigations²¹ and EMA's Reflection paper on eSource²² provide key input to expectations for sites and sponsors/CROs.

As a part of good software development life cycle (SDLC) practices, clinical researchers should encourage their eSource providers (e.g., EHRs) to implement the following recommendations wherever possible:

- controlled access
- appropriate, documented training of users, administrators, and developers of the eSource system
- written policies holding individuals accountable for information contained within the eSource application to which their signatures were applied
- requirements related to electronic signature compliance
- audit trails (user, date/time of data change, reason for change (if applicable), and all previous entries not obscured)
- documented system validation including system users, for example researchers, participating in user acceptance testing.

Sponsor/CRO data managers have the right skills and are in the best position to advise their organizations on a risk-based approach to evaluating sites' data systems to ensure they are meeting SDLC practices (checklists, defining roles and responsibilities, etc.).

4. Data Collection Modalities

While applying the above principles, consideration should also be given to challenges and solutions that are specific to a given eSource modality. The following sections address the most common eSource data collection modalities: third-party data, eCOA, EDC and EHRs.

²¹ FDA, US Department of Health and Human Services, September 2013, Guidance for Industry Electronic Source Data in Clinical Investigations. Procedural. [2013 Sep; cited Sep 2013] Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf>.

²² European Medicines Agency, 9 June 2010; EMA/INS/GCP/454280/2010; GCP Inspectors Working Group (GCP IWG). Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials. [2010 Jun 9; cited 2013 Sep 2] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf.

Third-Party Generated Sources (Central Laboratories, ECG Data, IRT, etc.)

We define third-party data sources as those electronic sources not controlled by the entity that requires the data to perform analysis and reporting for a clinical trial. Certain third party data, such as laboratory data and electrocardiograms (ECG), were among the first electronic sources adopted. Using these data as eSource has been successful because the processes to handle eSource from these organizations are well established; the technology is mature and data standards are available.

The influence of third-party data sources will continue to increase as technologies continue to advance, making data available much more quickly. The varied sources producing these critical data for research are not all necessarily regulated by government authorities. Organizations relying on these data to demonstrate effectiveness, safety, metabolic behavior, and/or post-marketing outcomes have adopted best practices to receive, exchange, manage, track, and store electronic data from third-party sources thereby demonstrating control and traceability. Regardless of the specific third-party data source, processes and principles for handling and maintaining these data should be consistent.

Process

- **Planning:** Before clinical trial data are collected in any third-party data source, planning activities need to take place. The entity managing the data source and the recipient of the data to be collected must agree on their roles and responsibilities during the life cycle of data acquisition, management, and archival. The overall dataflow, chain of custody, transmission data structures (naming conventions, data attributes, etc.) and issue resolution should be clearly documented in the Data Management Plan (DMP) or related documents. (See [Principle 2 Declare the source.](#))
- **Executing:** Executing third-party data acquisition and management should be in accordance with the approved plan. It is recommended that test data from the third-party data source be transmitted to the receiving entity to verify the data structures as well as the data extract and transfer process (including appropriate security measures to protect the data during the transmission). The receiving entity should execute a complete and thorough check to ensure that data from all sources are reconcilable and suitable for analysis. At minimum the subject and visit identifiers must be reconciled. Checking of safety and efficacy data across different data sources to ensure consistency of data handling may also be necessary. All programmatic checks and manual data review should be documented as part of the DMP or edit specifications documents. (See [Principle 5: Leverage automated quality checks.](#))

During the course of study data collection requirements may change as a result of a protocol amendment. The DMP and the data transfer specification should be updated accordingly if the changes result in new data present for only a subset of subjects (i.e., subjects already beyond the point in the study when the new or modified data are collected). A specific description of the expected disparity

should be documented in the DMP. Implementation of such middle-study change will require close collaboration by all parties.

In any scenario involving third-party generated data, it is critical that any data corrections deemed necessary are made at the source and not to subsequent copies of the data.

People

Depending on the organization and structure of companies, the people involved in the exchange of third-party data can vary. We outline the key functional roles that should be engaged in the life cycle of a clinical trial using third-party data: More than one of these roles may be held by the same individual in an organization, and the roles focus on the recipient entity.

- **Project Manager:** The Project Manager role may also be referred to as the Vendor Manager who oversees all aspects related to the third-party deliverables including contract, budget, meetings and minutes, data transfers, and archive documents at end of the study. The Project Manager will often liaise with the corresponding vendor's Project Manager to assure alignment of expectations.
- **Data Manager:** The Data Manager role focuses on the actual study data received from the third-party data source. The Data Manager owns and executes against the approved DMP and liaises with the corresponding data management personnel at the third-party vendor. The Data Manager provides information to the Project Manager pertaining to progress of activities against milestones and deliverables, impacts on specific changes and timely communication about any potential issues/challenges that may impact the ability to deliver data for the analysis and reporting of the trial. Documentation of data handling procedures and any deviations are the responsibility of the Data Manager.

Technology

As technology develops the number of third-party data sources is ever increasing. Below is a representation of some of the more notable sources commonly used.

Laboratory Data

As the most mature use of eSource, central laboratory services have been successfully used to analyze clinical safety (hematology, chemistry and urinalysis) and bioanalytical samples from clinical trials for decades. Why have they been so successful? The instruments are fully automated to perform the assays and to generate data. Data standards and control terminologies are well defined. Laboratory data are commonly included in regulatory submissions to support marketing applications. The laboratory instruments used to generate data for clinical trials must be US FDA 21 CFR Part 11 compliant and validated. Laboratory data can be accessible through Laboratory Information Management Systems (LIMS) by laboratory personnel or via a web-based portal to the physician and project team. The data are exported from the LIMS database and transferred to the sponsor/CRO through secure means for analysis and reporting. When central laboratory services are used, the investigative sites should intend to use the central laboratory for

regular, scheduled or non-emergency unscheduled blood draws. It is understood that some sites are required to use a local lab (e.g., a university site). The same requirements put forth to the central laboratory should be adhered to by the local laboratory. In the case of an emergency situation for patient safety reason and a local laboratory has to be used, a duplicate sample should be obtained and sent to the central lab for confirmatory analysis. (See Principle 6: Control for quality.)

Electrocardiogram (ECG) Data

Another commonly used electronic source in clinical trials is the collection of electrocardiogram (ECG) data to evaluate cardiac safety. Central vendors usually provide ECG machines to investigational sites participating in a trial. ECG tracings and Holter ECG measurements are periodically transmitted to central readers usually at the end of each day. The cardiologist at the central facility conducts the reading and provides ECG parameters and interpretation to the sponsor/CRO as electronic data files. For submission to the US FDA, electronic ECG waveform files in XML format may be also required. It is important to ensure that the ECG machines are compatible with the FDA data warehouse requirements. When a central reader is used to assess ECG results, sites should be cautioned not to use local ECG machines since it would be difficult to digitize paper tracing to combine the results with the rest of the data.

Interactive Response Technology (IRT)

Interactive Response Technologies (IRT) traditionally referred to as Interactive Voice/Web Response Systems (IVRS/IWRS) have long been in use in clinical research. The typical purpose of IRT has been to randomize patients and manage clinical drug supply. Because this paper focuses on eSource, we only examine the electronic data collection and use of such data to support regulatory submission.

IRT, like other electronic data collection systems, provides secure log on, audit trail, and transaction logging. To support clinical operational, demographic, enrollment and drug accountability, information is often collected real time in IRT while the subject is on site. The relevant data can be extracted from the IRT system and transferred as datasets to the sponsor/CRO or be integrated directly with other clinical data collection systems such as EDC. Integrating IRT with EDC allows the subject eCRF to be automatically populated with data, avoiding duplicate data entry of demographics, drug accountability, and other information, thus alleviating the need for reconciliation of data from two different sources. For EDC data collection where IRT is not integrated with EDC and is not electronic, a paper log is used as official source. In such a case, duplicate data collection may result in discrepancy between the EDC and IRT data. It is important that the official source be declared whether or not IRT is integrated with EDC. (See Principle 2 Declare the source and Principle 6: Control for quality.)

Sponsors should consider the complexity of data integration within the two systems early in the study setup. Since IRT integration must be completed before the EDC system can be used, it is paramount that all tasks are accounted for in the project timelines and robust project management is applied. Integration can be either one direction or both directions. One-way integration is to populate IRT data into

appropriate eCRF forms and data fields. Two-way integration will also include automated data transfer from EDC to the IRT system. It would be advantageous to use a system that provides internal integration between IRT and EDC modules.

In addition to the previously discussed electronic sources (Lab, ECG and IRT) there are many other types of data that are generated electronically and transferred directly as data files from third-party vendors. Examples of such third-party data include polysomnography (PSG) sleep data, neurocognitive test data, radiology and MRI image data, PET scan data, and pharmacogenomics data. The same considerations apply to these additional electronic source data. Imaging data are usually processed by a medical specialist. Sponsors/CROs may only receive data for overall interpretations or key parameters for reporting and submission. All third-party data will need to be reconciled with the data collected on the CRF to ensure integrity and consistency.

Electronic Clinical Outcome Assessment (eCOA, eDiaries, ClinRO, ObsRO) to Capture Patient-Reported Data

Electronic Clinical Outcome Assessment (eCOA) systems also known as Electronic Patient Reported Data systems are unique when contrasted with other sponsor/CRO-provided electronic data capture in that these patient-centric data collection methods capture the source data directly from the patients. Unlike EDC, an eCOA setup may require psychometric and cognitive validation of the instrument or questionnaire. Additionally, eCOA allows direct transfer of data generated from other patient devices such as personal glucometers and peak-flow meters.

In the context of this paper, eCOA includes collection of both the copyrighted, validated instruments such as Quality of Life SF-36, Montgomery-Asberg Depression Rating Scale, and so on, as well as any diary data collected directly from the patients. The data collected in this context are the eSource data.

In today's clinical research industry, eCOA system development is typically a joint effort between the sponsor and a sponsor-sourced third-party eCOA provider. A data collection modality such as a smartphone, tablet, etc., can be provisioned and provided to the patients, investigators, or the caregivers or alternatively, they can bring their own device. The data are electronically entered and edit checks executed at the time of data entry. Once data are successfully entered, they are transferred to the third-party eCOA provider's database server where the eSource can be accessed by the sites and sponsor/CRO personnel according to and based upon their role within the trial. At the end of the trial, the eSource is copied on a durable media (e.g., DVDs) and sent to the clinical sites and sponsor/CRO. Upon confirmation that the eSource is in the sites' possession, the third-party eCOA provider decommissions and archives the eCOA database. The diagram below represents the key aspects of an eCOA setup.

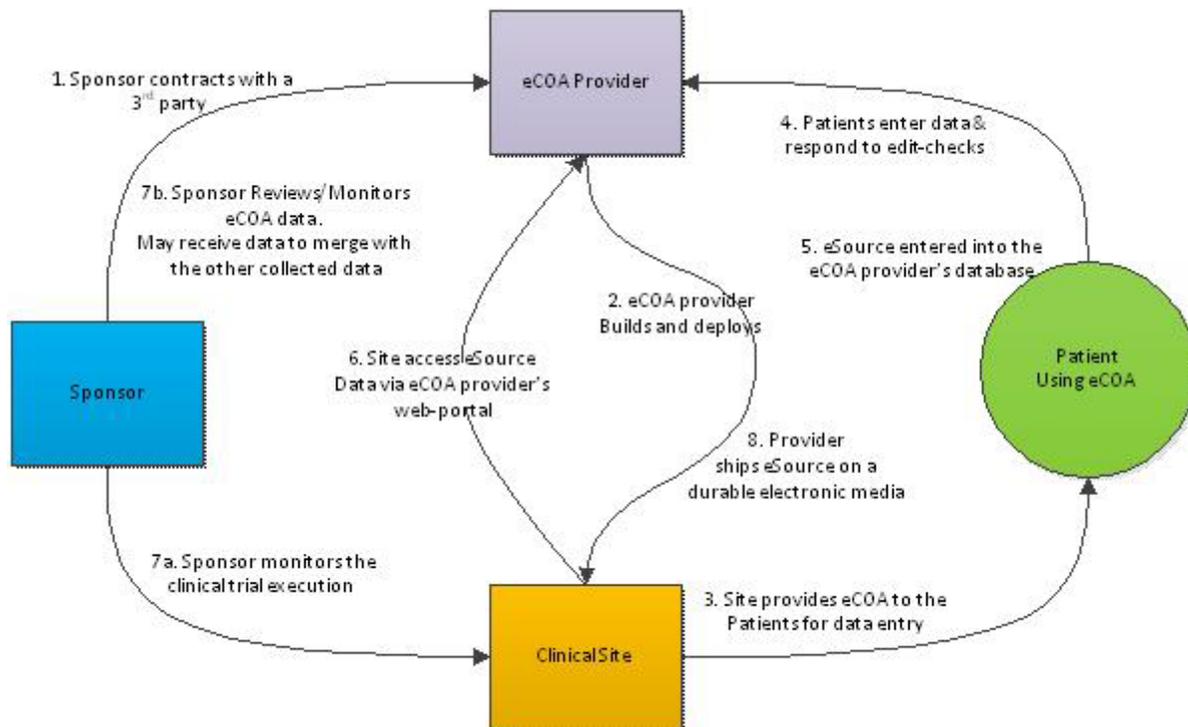


Figure 2: Electronic Clinical Outcome Assessment (eCOA)—Traditional Setup Process

- Planning:** Sponsors should define all patient data collection instruments early in the clinical trial planning stages. All eCOA data to be collected must be driven by the clinical trial protocol and be fit for purpose. In certain cases, it may be necessary to implement additional rigor to the measurement validation such as cognitive debriefing or linguistic validation. If a copyrighted measure is used, an approval to use it should be obtained. These activities require working with one or more external providers and can add additional timeline risks to eCOA deployment. (See Principle 1: Use solutions that are “fit for purpose”.)
- Regulation:** Although we do not intend to discuss all the specifics of the current and active regulations that cover electronic data capture, it is to be noted that the US FDA 21 CFR Part 11 and the FDA’s Guidance for the Industry: Patient Reported Outcome Measures: Use in Medicinal Product Development to Support the Labeling Claims (Dec 2009)²³ apply. (See Principle 6: Control for quality and Principle 7: Conform to regulations and guidelines.)
- Dataflow:** Due to practical reasons, at the time of protocol writing, the eCOA dataflow may not be completely known; however, the sponsor Data Management

²³ FDA, US Department of Health and Human Services, December 2009, Guidance for the Industry: Patient Reported Outcome Measures: Use in Medicinal Product Development to Support the Labeling Claims [2009 Dec; cited 2013 Sep 2] Available from: <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>.

Plan (DMP) should clearly articulate the description and flow of the patient-reported data that is captured as eSource. In other words, it should describe how the eSource data would be electronically transferred from the patients' hand-held devices to the eCOA provider's data center and integrated with other clinical data collected through the EDC system by the sponsor/CRO. It is important to note that eSource data once transferred from the eCOA device, resides at the third-party server, and the sponsors/CROs only get a copy of the data for processing. eSource is not *moved* to the sponsor/CRO.

People

- **Sites:** Clinical investigators should have access to the eCOA data at all times. It is important to note that unlike other eCRF data that is transcribed from a source document and entered into the sponsor/CRO-provided EDC system, eCOA data is the eSource and therefore the site investigator's approval of the accuracy of eCOA data captured is not required. Nevertheless eCOA data should be monitored by the sites to ensure patients' safety at all times. The eCOA system should be developed to send alerts to site personnel and clinical safety monitors when peculiar eCOA data pointing to a safety concern is entered. (See Principle 4: Control electronic data.)
- **Sponsor/CRO:** The eSource data collected via the eCOA system is unlike any other transcribed eCRF data and therefore should not be queried and cleaned in the same manner. Sponsor/CRO review and query of the source data should be planned in advance and be kept at a minimum, for example, subject identifiers or seeking clarification on data points that may point to safety issues. Most, if not all, data entry errors should be caught during the electronic capture of the eCOA data, however in those rare instances where an erroneous data point needs to be updated, the sponsor/CRO should follow the eCOA provider's data correction process, which should have a provision for the site's review and approval. Electronic prompts, flags and data quality checks should be used to minimize errors and omissions at the time of data entry²⁴. (See Principle 5: Leverage automated quality checks.) Due to the element of "recall bias", data entry time windows should be established and queries should be created as close to reporting of the event as possible. Because the key benefit of eCOA is improved data quality, sponsors/CROs also should carefully weigh the downside of allowing lengthy retrospective data entry periods. Due to the lack of traceability or audit trails outside a controlled system, when eCOA is used, sponsors/CROs should not allow capture of the same eCOA data via other paper source; for example, data transcribed on paper and brought to the site. Lastly, it is important to note that although an eCOA implementation contract is established between the sponsor/CRO and the eCOA provider, the contract terms should clearly lay

²⁴ FDA, US Department of Health and Human Services, November 2012, Guidance for Industry Electronic Source Data in Clinical Investigations DRAFT GUIDANCE. Lines 215-216.

out the independence of the eCOA provider for hosting the eSource data and that source data is in the exclusive control of the investigator²⁵ (See Principle 5: Leverage automated quality checks, Principle 3: Capture data when first generated and Principle 2: Declare the source.)

- **eCOA Vendors:** eCOA vendors play a key role in ensuring the independent nature of eSource data. eCOA providers should have a documented process and procedural controls to demonstrate that all data edits or corrections are documented and approved by site personnel. This should be in addition to the audit trail, which should be part of the system. eCOA vendors must ensure the availability and accessibility of eSource data by the sites and the sponsor/CRO at all times. They should publish the system maintenance periods and communicate any downtime periods to site and sponsor/CRO personnel. Vendors should also provide documentation including a dataflow to the site with regard to how sites meet US FDA 21 CFR Part 312.62(b) to maintain case histories using this method. (See Principle 4: Control electronic data, Principle 3: Capture data when first generated and Principle 6 Control for quality.)

Technology

- **Modality independent eCOA:** Continued pressures on cost containment within the clinical research industry as well as rapid adoption of consumer mobile smartphones and tablets are creating opportunities for sponsors/CROs and eCOA vendors to look for ways to reduce costs by utilizing the patient's own mobile phone, laptop, and tablet to collect eCOA data. According to the Nielsen Survey, overall smartphone penetration in the US grew from 45% in the fourth quarter of 2011 to 60% in the fourth quarter of 2012. Smartphone penetration among people who recently bought a mobile phone stood at a whopping 77% in the fourth quarter of 2012.²⁶

Although smartphone adoption opens up new doors and opportunities to implement more cost-effective eCOA data collection, it also raises unique challenges. First and foremost, the eCOA instrument's validity on different mobile platforms as well as rendering on different screen sizes becomes a big question. Secondly, this can introduce operational management challenges at the site where a site would now have to ensure each device make/model/operating system meets the requirements to be used as an eCOA device.

²⁵ European Medicines Agency, 9 June 2010; EMA/INS/GCP/454280/2010; GCP Inspectors Working Group (GCP IWG). Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials. Topic 3: Control. [2010 Jun 9; cited 2013 Sep 2] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf.

²⁶ The Nielsen Company (www.nielsen.com). Mobile Insight Q4, 2012.

Even with the aforementioned challenges, which are directed more toward copyrighted, validated scales and instruments, modality-independence can be a solution for post-marketing trials or to capture simple patient diaries. Therefore, a “fit for purpose” approach is warranted. (See Principle 1: Use solutions that are “fit for purpose”.)

Sponsors should discuss any modality-agnostic eCOA data capture ideas within their program with regulatory agencies as early as possible, for example at the End of Phase II meeting. eCOA vendors and sponsors/CROs should ensure that the data collected from different modalities reside in one centralized database.

Sponsor/CRO Electronic Data Capture

Using EDC as an eSource system requires a paradigm shift from the current transcription into EDC being used today in the majority of studies. When using EDC as eSource, Principle 4 Control electronic data, can be satisfied via the rights/roles/privileges functionality inherent in the EDC system. Multiple aspects of process, people and technology changes outlined below must be in place for EDC to be considered eSource.

Process

- **Point of Care**— eSource requires contemporaneous recording. However, depending on the procedure or when enrollment is determined, direct data entry may not be possible (e.g., enrollment based on an investigator’s decision during an open surgical procedure). In this situation, routine paper source guidelines are to be followed. In general, the site should indicate which data points are transcribed from original paper source documentation versus data points that are eSource. One example of how to achieve this is to use a direct data capture system that allows fields to be flagged if they are sourced from paper. Any application that can be used on a mobile device should increase the site’s interest in Direct Data Entry into EDC. (See Principle 3: Capture data when first generated.)
- **Data entry instructions** are critical and could be in the form of completion guidelines or help menus built into the electronic system.

People

- **Investigational/Clinical Site**
 - **Clinical Coordinator Experience:** As eSource becomes a more common practice for capturing data, the opportunity to lose data due to incorrect readings, typographical errors, or common mistakes increasingly becomes a major concern. If the correct data are not captured or entered during the interview with the subject, that information may be lost permanently. Due to this, sites instructed to capture clinical data in an eSource system should make special considerations to have an experienced coordinator, nurse, or designee perform or oversee the data entry to ensure data are captured accurately and represent the status of the subject during the

interview period. The person assessing the patient should be the person entering the information or overseeing and/or reviewing the entry of the information into the electronic system storing the clinical data.

- **Technical Ability:** When considering executing clinical research where the eCRFs will be source data; special consideration should be taken to ensure the investigational site can accommodate capturing data electronically at the point of care. Sites should be assessed on their ability to enter data in real time and a thorough assessment of their ability to connect to the EDC system during a patient interview should occur prior to selecting the site as part of the study. If reliable connectivity is not available, an alternative method of capturing data manually and performing data entry at a later time should be considered. Assessments should reflect the local feasibility of the modality employed. A checklist for appropriate assessment areas is recommended to maintain consistency when assessing multiple sites.

- **Sponsor/CRO Monitors**

- **Traditional Monitoring:** Although eSource may make some forms of source obsolete, sponsors and their designated staff should be vigilant to maintain compliance by recognizing when clinical data capture is part of another source system (laboratory devices, medical records, patient charts, etc.). In this case, traditional source document verification should be performed on critical data points that affect the primary endpoints, secondary endpoints, and safety results of the subject. Processes to verify the existence of patients should continue to be used.
- **Remote Monitoring:** A truly electronic source clinical study leaves little to no paper for a monitor to reference on a traditional monitoring visit. Given this drastic change in their traditional monitoring processes, monitors should now view remote monitoring as their optimal solution. Remote monitoring (along with Targeted Source Document Verification (TSDV) or Risk-Based Monitoring (RBM)) allows the monitor to review data for potential queries, discrepancies, etc., without the additional resource, travel, and financial burden previously considered routine. For additional details on remote monitoring, see the FDA's Guidance for Industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring²⁷
- **Reliance on Data Quality Checks:** As monitors shift from paper to eSource, their reliance on clinical edit checks becomes significantly more

²⁷ FDA, US Department of Health and Human Services, August 2013, Guidance for Industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring. Procedural. [2013 Aug; cited 2 Sep 2013] Available from: <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf>.

important. With the appropriate edit checks, the burden on monitors and data management should be reduced throughout the life of the study allowing for faster database locks, shortened clinical study closeout, and reduced travel required throughout the study. (See Principle 5: Leverage automated quality checks.)

Technology

- **Data Quality Checks (Edit Checks):** Given that the EDC system will now be the source for clinical data, there is very little room for error. As research moves to eSource, edit checks become very important for the quality of data being captured. Edit checks should be in place and thoroughly tested prior to subject enrollment to ensure that as data is being captured, the edit checks are executing and responding with the appropriate query, range check, format checks, and so on.
- **Data Access:** Traditionally, EDC systems are web-based systems. In a true eSource environment, care must be taken to ensure that the data capture system is “live” and accessible to the clinician during the subject visit regardless of Internet access. For example, in a study using EDC as eSource, the data capture interface needs to be available during all parts of the subject interview and visit. In most instances, it should be mobile to capture data at the point of care.
- **Connectivity to External Systems:** The sponsor/CRO should also consider alternative (fail-safe) methods of capturing data in the event the EDC system cannot be accessed during a subject’s visit period. In the case of time-critical data (i.e., SAE reporting), a backup may be necessary in the event of a system failure. This will allow data to be stored and entered at a later date when the system is fully restored.
- **Enduring:** Backups of EDC are necessary to ensure no loss of eSource data. Each company should have a risk-based approach as to how frequent servers are backed up given this is the only copy of the data. (See Principle 6: Control for quality.)

Site Controlled EHRs

In the EHR operating paradigm the segregation of duties is quite clear. The clinician, the clinician's practice or institution own and manage the EHR for the primary purpose of providing direct care to their patients. Those business practices are governed by different regulations but still require similar control systems to manage the records and assure they substantiate the history of care. (See Principle 4: Control electronic data.)

Given the relatively nascent nature of EHRs, there are myriad implementations and the global marketplace has yet to settle on a stable, effective solution to exchange EHR’s clinical data with clinical research. Thus, it is likely that for some time investigators will manually have to transcribe data captured in an EHR into the clinical research data capture tools, be they paper or EDC technology. A direct feed from the EHR to the EDC tool is currently limited to a few real-life examples. This paper entertains both paradigms. (See Principle 3: Capture data when first generated.)

Transcribed EHR to EDC

In this transcribed scenario EHR functions similarly to the paper patient chart and thus the roles of the sponsor/CRO clinical trial monitor and regulatory inspector change very little. They still require the ability to read patient records to verify the transcription of data (into paper CRFs or the sponsor/CRO EDC system) is accurate. The primary difference is simply that they require different training to effectively and appropriately access the EHR rather than the traditional paper records.

To meet regulatory expectations, if the EHR is used in any capacity, the subject's records from the EHR should be accessible to the monitor and inspector either through direct access or together with site staff. Such obligations need to be clear when screening investigators/sites for clinical trials and supported in the research contracts. It should be noted that in the certified copy paradigm, the certified copy coexists with the eSource. Any changes to the data should be made at the eSource, that is, in the EHR. Understanding the starting point for sponsors/CROs to evaluate sites' systems is key to appropriate evaluations. (See Principle7: Conform to regulations and guidelines.)

Can We Eliminate Manual Transcription from EHRs?

Given that manual transcription of data from an investigator's EHR to a sponsor's/CRO's data capture system replicates many of the risks of manual transcription from paper records, FDA guidance²⁸ acknowledges that transcribing data from an EHR onto either paper or electronic CRFs is not the goal of eSource technology. The more favorable alternative would be direct/auto transfer of relevant EHR data to the sponsor's/CRO's clinical research systems. One problem is the limited "ability to communicate and exchange data accurately, effectively, securely, and consistently with different information technology systems, software applications, and networks in various settings... such that clinical or operational purpose and meaning of the data are preserved and unaltered".²⁹

However, this is not as simple as exchanging data. The CRF logically guides the clinician to what data to collect at each visit and supports capture and reporting of adverse events. Thus, replacing the CRF requires substantial process integration as well as data exchange. In an effort to support data transfer from EHRs for research purposes, CDISC and IHE (Integrating the Healthcare Enterprise) developed an integration profile to collect and transfer key clinical trial data already existing in the EHR to an EDC. Demonstrations/pilots at Healthcare Information and Management Systems Society (HIMSS) and Drug Industry Association (DIA) conferences have been

²⁸ FDA, US Department of Health and Human Services, September 2013, Guidance for Industry Electronic Source Data in Clinical Investigations. Procedural. [2013 Sep; cited Sep 2013] Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf>.

²⁹ FDA, US Department of Health and Human Services, February 2012 [Revised February 2014], Guidance for Industry Providing Regulatory Submissions in Electronic Format-Standardized Study Data. Available from: <http://www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf>.

successful and one EHR vendor expanded on that concept to integrate their hospital EHR with their clinical research data capture tool. The premise is to populate the CRF with data collected in the EHR, surfacing the CRF within the EHR. There is still a person verifying the data for research is correct and then it is also archived as the certified copy of eSource and saved per legal requirements. Updates to the EHR are resent to the CRF and archive.

Interoperable EHR/EDC

Process

- During the design of the eCRF, the data manager must work with technology colleagues to identify which elements are to be entered by site staff, and which elements will be extracted and transferred to the eCRF electronically so that the database can be set up to accept transfers from the EHR system to populate the CRF. This mapping exercise is facilitated if the EHR vendor can produce Health Level Seven (HL7) v.2 output (e.g., Continuity of Care Document (CCD)) and has experience with integration profiles such as Retrieve Form for Data Capture (RFD). In addition, documented processes for handling amendments and other changes that can affect the fields collected in the EHR system and the eCRF must be in place. (See Impact of Amendments section.)
- Documentation must be kept that outlines what fields on the CRF are manually entered by the site versus what fields are electronically transferred from the EHR to the eCRF. The DMP is the most likely place to document these study-level conventions, and additionally a site-level source document is needed to identify how the site will capture source (eSource-EHR, direct data entry into EDC tool or paper transcription). (See Principle 2: Declare the source.)
- At database lock, a process to disable further transfers from site EHR systems must be implemented in addition to the traditional locking of case books. It is recommended that a process to verify all EHR data has been transferred to the EDC system, if the EDC/EHR integration does not already provide this information.

People

- As in any change management, behaviors will be the hardest to modify. Site personnel such as study coordinators and principal investigators will be more willing to adopt a model that closely integrates their EHR with an EDC tool, thus providing one familiar interface and allowing for a shorter adoption curve. However, if the tool is not customized to the site's workflow, the adoption/satisfaction rate will be low. Fewer mouse clicks to navigate and visibility to patient status at all times will facilitate workflow. Functionality that supports both the patient's healthcare activities and research requirements is key.
- Given the highly technical nature of the integrations, an alternative model with a third party may be the most effective in setting up the transfers versus site personnel. A new role of central monitor would also benefit from a direct feed from an EHR to an EDC in that source document verification (SDV) at the site location would be dramatically reduced and remote monitoring enabled.

Additionally, with EHR access, remote monitoring or inspections to ensure completeness of the CRF records would be possible.

Technology

- Technology solutions are only possible when the content to share is semantically interoperable. Standards are critical to enable data sharing between systems. Even if each system brings different standards to the table, they can be mapped for integration. When there are no standards, customization becomes too prohibitive for interoperability. For healthcare, Health Level 7 (HL7) is the standard; for research it is CDISC. The CDISC Biomedical Research Integrated Domain Group (BRIDG) model brings the two together by starting with concept modeling to ensure semantics are correct.
- When importing data from an EHR system into an EDC system consider:
 - The vendor of the EHR system at each site (some vendors have built-in integration functionality, some have customized integrations), how the system handles exporting information, and the capacity of your EDC system to handle the load transactions from multiple sites on an ongoing basis.
 - Traceability should be maintained between the EHR system and the sponsor/CRO database. (See Principle 6: Control for quality.)
 - The sponsor's/CRO's database must be designed to accept and denote multiple data entry methods: direct site data entry, transfer from EHR systems and other external sources to support the collection of eCOA or central laboratory data.
- Edit check design
 - Consistency checks on the data transferred from the EHR must be handled differently than those designed strictly for use on data captured in EDC. Consider employing analytical tools to look for corroborating evidence within the case report form if data anomalies are detected. For example, treatments associated with a given condition reported as a clinical finding. (See Principle 5: Leverage automated quality checks.)
 - Data quality checks take on more significance for data collected via the EHR and transferred to the EDC system. Checks for missing information, inconsistent dates, and so on, should be included in the overall data management plan. (See Principle 5: Leverage automated quality checks.)

This section explored an interoperable EHR/EDC however the same principles and best practices apply to a tablet-to-EDC model. This model is an interim solution in which a third-party IT vendor supplies the site with a tablet to collect eSource that could directly feed a copy to both an EDC system while providing an archivable file to store in an EHR (e.g., PDF). This interim eSource solution requires an investigator-controlled database hosted by a neutral third-party IT organization for the eSource collected in the tablet. Data management activities are limited to checks programmed on the EDC system.

Impact of Amendments on EHR, Edits, etc.

Amendments to protocols pose a challenge similar to those encountered with the current state. Changes still need to be managed through a robust change control process. The difference is that the site or perhaps a data broker would now be included in the technology changes as the mapping from EHR to EDC would be necessary. For edits, the changes would still be added to the EDC as they are today—contained solely within the sponsor/CRO realm.

5. Future Directions

The future of leveraging eSource efficiently lies in integrating the modalities described in this paper.

Standards, both format and content, are the key to integration and eSource information sharing. Standards organizations such as Integrating the Healthcare Enterprise and CDISC are working on profiles to enable data sharing across multiple sources. Without standards, an integrated future is limited and would require extensive custom mapping.

Technology advances and regulatory encouragement have converged to move the clinical trial industry to the tipping point for more widely adopting eSource. Progressive organizations that are preparing now for adopting eSource must assess the challenges that will impact their processes, people and technologies.

Process

- eSource turns the paradigm of the paper process for clinical trials on its head. To continue progress and realize the full benefit of eSource, we must change our mindset from the old paradigm of paper to the new paradigm of data integration throughout the trial. Every facet of the process must be evaluated and we must be ready to adapt or retire existing processes, and adopt or create new processes.
- The Data Management Plan will become even more critical to the success of data management as the dataflow becomes more complex and the chain of custody and traceability become automated. DMPs should be authored by a data manager who fully understands the dataflow, data sources, and the procedural adjustments needed for each type of source. For example, the data verification process needed for data that have been collected from an eSource through 100% electronic transfer would be very different than for data collected in EDC through manual transcription.
- Dataflow and chain of custody will affect our approach to Risk-Based Monitoring as well. For example, source data verification will be obsolete in a 100% electronic transfer of data from an EHR, whereas in a process where the site is performing manual transcription from the EHR to an EDC system, RBM would include some level of defined source data verification. Dataflow will help focus on what controls and processes are required to ensure data integrity.

People

- In all of the role changes from data manager to monitor to project manager, the role of the data manager remains vital and crucial to the task of providing a data set that is fit for analysis. Data managers must understand the complete life cycle and flow of data, from the point of collection through the point of reporting. Their role will include managing the dataflow and integration of data from various sources in such a way that data integrity and traceability are maintained.
- The data manager's role will evolve from one of being primarily a data reviewer, to one of managing the processes and technologies that allow eSource to become integrated in the clinical trial process. As the focus of monitoring shifts from source data verification to ensuring site compliance with the protocol and with Good Clinical Practice, the data manager will be crucial to the development of technology and process solutions to support risk-based monitoring.
- Although technologies and processes will certainly evolve over time, the underlying responsibility of data management remains the same: to deliver a set of data that are reliable and fit for use. We must be ready to meet the challenges of our responsibilities in a rapidly changing technology landscape that is unlikely to stop evolving any time soon.

Technology

- Emerging technologies are and will continue to be the driver for the availability and adoption of eSource in clinical trials. It is impossible to predict what future technologies will be developed to support eSource. To ensure eSource for clinical trials is maintained under appropriate controls, standards and processes must be continuously assessed and adapted. The concepts and principles presented in this paper form a solid foundation ready to be adapted and leveraged across trials as new eSource technologies evolve.
- Validation of the integrations between the site EHR and the sponsor/CRO data collection system is important. Validation processes should be based on the type of integration. Given that each EHR is different and has numerous upgrades/releases, one way to significantly reduce the validation of the transfer process would be to include a human verification step of the data auto-populating the eCRF—essentially a manual validation with each population. For example, if a common integration with the sponsor/CRO data collection system is possible with an EHR product, one validation per EHR system can be applied to all sites using that particular EHR system. Otherwise, develop a strategy to ensure the integrations are working as expected with each site. In a future-looking option, this may best be done with a newly formed type of entity called a data broker. This data broker could act as an intermediary for EHRs and EDCs for all clinical researchers. The data broker would validate the transfer process and keep up to date with any new releases of EHR software that might impact validation. They would also map core data fields (CDASH) from an EHR to a CRF and the clinical researcher

would buy these services. The data broker could also be an archivist for the site (a role in RFD) and could operate in a community cloud where multiple sponsors/CROs could access the shared validation or mapping information. The study archived data could reside in a private cloud for the site with view-only access for sponsors/CROs or inspectors thus meeting the requirement that the sponsor does not have control of the source data.

- An unconventional but effective approach to further segregate controls would be to have commercial software (the application, not a person) digitally sign all records as they are written to a database which would prevent the investigator, sponsor/CRO or any third party from creating or modifying data outside of the commercial software without detection.
- Organizations also need to address data integrity considerations when collecting data through various eSource technologies. Although validation of the actual eSource technology at the site may be out of the scope of responsibility for sponsors/CROs—just as validating a paper source process would be—the processes for capturing data from the eSource will need to be validated, and the methodology of validation will differ based on the modality.
- Assessing the value and appropriateness of a new technology is also challenging and its mere existence should not translate into its adoption, or that it should be implemented for every trial—there is no “one size fits all” in selecting eSource modalities to use in a trial. Each clinical program and trial must be individually evaluated to determine which eSource technologies should be leveraged.

6. Conclusion

The benefits of eSource are far reaching. In the scenario of direct patient data capture, an eSource is virtually the only method that assures contemporaneous data capture with corresponding audit trails to assure the principal investigator, sponsor/CRO and regulators that data were captured in compliance with the protocol and data handling instructions. When data are captured outside the confines of a site visit, and hence outside the direct control of site personnel, protocol adherence should be a critical concern. In such a setting, eSources such as eCOA become significant adherence and risk mitigation instruments.

Across all aspects of source data generation, paper can no longer be considered the “gold standard.” Demanding high-quality data should be the gold standard—a modality that can help improve it should be the right choice. The minimization of transcriptions (and inherent errors), the data association to individuals and timestamps offered by audit trails, the data validation enabled by automated system queries and the potential for virtually instant safety review to protect human health are more than adequate justifications to establish eSource as the new “gold standard.”