Practical Considerations for Clinical Trial Sites using Electronic Health Records (EHRs) in support of Clinical Research

Addressing Regulatory Considerations

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EHRCR (Electronic Health Records for Clinical Research) Working Group
Sponsored by eClinical Forum and PhRMA EDC/eSource Task Group

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i. Foreword

An increasing number of healthcare institutions are employing Electronic Health Records (EHRs) to maintain patient records. Clinical research draws on a combination of data collected during the course of a clinical trial and historical medical information relating to the research subject(s). As many institutions involved in clinical research begin to transition to the use of EHR systems, a growing amount of source data for clinical research is originating from these technologies.

The Electronic Health Record for Clinical Research (EHRCR) Project was organized in December 2006 at the invitation of the Health Level Seven (HL-7) Technical Committee and EuroRec (see Appendix 2, References, Section 4). The project objective was to define requirements to expand and adapt the functionality of EHR technologies, including the associated systems, networks, and processes, in order to support the needs of regulated clinical research[1].

The EHRCR project team has produced a number of deliverables[2] including a ***User Requirements document*** outlining the project vision of fully integrated healthcare (eHealth) and research (eResearch) systems. In addition, an ***EHRCR Functional Profile*** delineates the high-level requirements necessary for EHR systems to be considered as a reliable data source in line with the appropriate regulations governing clinical research. This Functional Profile will be used as the basis for ***Certification of EHR systems*** used in clinical research with the aim of increasing the level of comfort of practitioners, the research community and regulators with the practice of storing source data in EHR systems.

The first step in establishing the EHRCR Functional Profile was to identify the 'Core Requirements' needed for EHR systems to meet current, fundamental clinical research requirements based on existing regulations and guidances (please refer to EHRCR User Requirements document and Addendum for further detail). Once identified, these requirements were refined into the criteria that make up the EHRCR Functional Profile. The profile was created based on the HL7 EHR Functional Model and the EuroRec EHR Repository – both are references of functions described from a user perspective that enable consistent expression of features that may be present in an Electronic Health Record System (EHR-S), independent of specialization, region or country.[3]

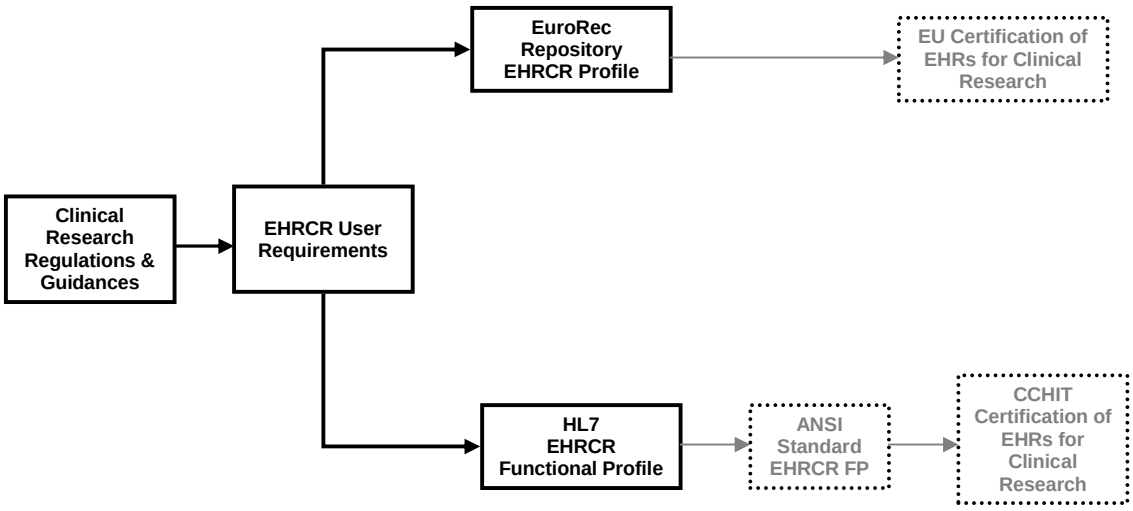
The EHRCR User Requirements & Functional Profile is provided in formats supporting both the HL7 EHR Functional Model and the EuroRec EHR Repository, and incorporates a mapping between these standards. The HL7 version was approved in the Unites States as an HL7 Informative profile in May 2008 and as an HL7 Normative profile in Jan 2009.

[1] The project team is made up of members from biopharmaceutical companies, clinical research system and healthcare system vendors, and regulators from both US and Europe. For more information on the project, please see our website: www.ehrcr.org.

[2] These documents can all be found at www.ehrcr.org.

[3] Both the HL7 EHR-S Functional Model and the EuroRec EHR Repository are also the basis for other functional profiles that describe features necessary and/or desirable for specific setting (for example intensive care, cardiology, office practice).

HL7 will be submitting this to the ANSI (American National Standards Institute) to become and ANSI standard. Additionally, this team is intending to participate in a committee to develop an EHRCR certification via CCHIT (Certification Committee for Health Information Technology) in 2010. In Europe, EuroRec has accepted elements of the EHRCR profile which were not already included in their EHR Repository. The EuroRec version of the profile is being formulated as a subset of the EuroRec Repository which will then also be offered to as a possibility for certifying EHR systems in Europe.



By using EHR systems certified for clinical research, sponsors, regulators and investigators can be confident that the integrity of clinical research data can be protected and that source data are stored in a manner compliant with clinical research regulations while minimizing process redundancy.

However, certification of EHR systems for clinical research is not sufficient. Research sties will need to implement and use such systems in a manner that complies with the regulations and guidances. *The purpose of this guide is to support individuals in configuring certified (or certifiable) technologies in a compliant manner*.

1 Purpose of this guide

This document is intended as a practical guide to assist clinical investigative site personnel in:

- Understanding and anticipating expectations when participating in clinical research (regardless of whether they are using an EHR system)
- Selecting or upgrading an EHR system to hold data which could potentially become source data to support regulated research work for drug or medical device clinical trials or development activities
- Identifying best practices in implementing and maintaining an EHR system, especially if it may hold data that could become source for clinical trials

A checklist is provided to identify site activities in selecting and implementing EHR software suitable for use in clinical research. While this document presents one approach a site may use to meet the expectations of the research regulations, it should be understood that any technical and procedural solutions should be implemented in the context of a risk assessment (see section 5.1).

2 Why should this information be important to you?

The US Food and Drug Administration (FDA), the European regulatory authorities and International Conference on Harmonization (ICH) provide requirements for clinical trial records, and the systems and processes that maintain them. References to these regulations and guidances are in Appendix 2 and specifics on how they relate to computerized systems are shown in the table in Section 5.2.

The same responsibilities of the investigator toward the accuracy of source data (meaning it is attributable, legible, contemporaneous, and original) exist whether those data are hand-written on paper or entered and stored electronically. Additionally, if data is entered and stored into an Electronic Health Record (EHR) system or Electronic Data Capture (EDC) system as the sole source and used in regulated clinical research, that system must be compliant with these regulations (for example, data in EHR / EDC systems that are used as eSource for clinical trials, under current regulation, require authority checks such as ensuring that only authorized persons can access the system, and maintaining a clinical research-compliant audit trail).

The ideal environment provides non-redundant systems and processes that allow the use of patient electronic medical data for clinical research in a way that meets data protection, regulatory, and ethical research requirements and minimizes the challenges of clinical research for healthcare professionals. This environment would include regulated clinical research in the natural workflow of a clinical practice thus providing tremendous benefit (to all stakeholders) with minimal impact to the healthcare provider.

As EHRs become more widely utilized and more sophisticated, healthcare providers will begin to seek functionality that will add value beyond the core functions related to the provision of healthcare. The re-purposing of healthcare data for quality reporting, quality improvement, outcomes assessment, and research will become a vital part of standard medical practice. Healthcare providers will eventually need EHR systems that support and facilitate these functions and EHR vendors will respond accordingly.

For more information on this topic, this project team recommends a discussion paper prepared by the eClinical Forum and PhRMA EDC/eSource Taskforce ("*The Future Vision of Electronic Health Records as eSource for Clinical Research*", September 14, 2006) that can be downloaded from www.ehrcr.org (in the Documents section). Although this paper is two years old, it is still very relevant and describes the benefits to patients, healthcare providers and clinical research, of connecting healthcare and research.

3 Applicable EHRCR Regulations and Guidance

The EHRCR User Requirements (included in abbreviated form in Section 5.2) are based on the following applicable clinical research regulations and guidances.

3.1 FDA 21 CFR Part 11

While the regulated clinical research community has had much discussion regarding 21 CFR Part 11, Electronic Records and Signatures Rule, (referred to as "Part 11" below) since its release by the FDA in August 1997, for the most part the healthcare community has assumed that it did not apply to them. As more and more electronic healthcare systems are holding source data that are used for clinical research, this argument becomes difficult to make. However, Part 11 is not something that should be feared by the healthcare community. It is a very valuable tool for maintaining and protecting the integrity of electronic records --- certainly something that is desired of all systems used to make decisions on patient health. We believe that the healthcare community is already voluntarily holding themselves to similar standards.

Part 11 was released in August 1997. The FDA also issued a clarifying guidance in 2001. According to the FDA Guidance for Industry: Part 11, Electronic Records; Electronic Signatures - Scope and Application:

> Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations. Part 11 also applies to electronic records submitted to the Agency under the Federal Food, Drug, and Cosmetic Act (the Act) and the Public Health Service Act (the PHS Act), even if such records are not specifically identified in Agency regulations (§ 11.1). The underlying requirements set forth in the Act, PHS Act, and FDA regulations (other than Part 11) are referred to in this guidance document as *predicate rules.*

The predicate rules that Part 11 is referring to incorporate the Act, the PHS Act and specific regulations around clinical trials (21 CFR Parts 50, 54, 56, 312, 314, and 812). Therefore, clinical investigators that participate in clinical investigations involving FDA-regulated devices and drugs are required to comply with these applicable statutes and regulations (regardless of their involvement with electronic records). These are intended to ensure the confidentiality, integrity and availability of clinical data and help protect the rights, safety, and welfare of human subjects.

Much like the other regulations cited in this document, Part 11 is not a passive regulation. Part 11 requires both technical and procedural solutions for a site to fully meet the spirit of the regulation.

Finally, if a clinical investigator site is located outside of the US, Part 11 may still apply if the data is being generated to support an FDA filing. The FDA can and does routinely inspect sites outside of the US for compliance to regulations. Furthermore, other countries and regions have similar laws for electronic record use (e.g., EU Annex 11).

3.2 EU Annex 11

Annex 11 is the abbreviation used by the Pharmaceutical industry when referring to *'EudraLex - The Rules Governing Medicinal Products in the European Union. Volume 4 - Guidelines for good manufacturing practices for medicinal products for human and veterinary use. Annex 11 - Computerized Systems'*.

EudraLex consists of 10 volumes, volumes 1 (human) and 5 (veterinary) contain the legislation and the other 8 volumes consist of guidelines to support the legislation. Volume 4 contains 9 chapters describing good manufacturing practices, and 20 annexes covering specific areas of detail. Annex 11 is presently only available in English, is draft and consists of 3 pages of guidelines. The guidance was released as draft for comment in April 2008 until October 31, 2008.

The principles of EU Annex 11, as stated in the draft guidance, are;

> "The introduction of computerized systems into systems of manufacturing, including storage, distribution and quality control does not alter the need to observe the relevant principles given elsewhere in the Guide. Where a computerized system replaces a manual operation, there should be no resultant decrease in product quality or quality assurance. Consideration should be given to the risk of losing aspects of the previous system which could result from reducing the involvement of operators."

Though EU Annex 11 is new for the regulated clinical research industry in Europe, the principles and guidelines are already well understood and largely met by adherence to 21 CFR Part 11. EU Annex 11 presents guidelines concerning personnel, validation and the systems themselves.

Like Part 11, the Healthcare Industry may believe that Annex 11 does not apply to them. But that argument is becoming more difficult to make as EHR systems increasingly store

amounts of electronic source data used for Clinical research. As explained above for Part 11, Annex 11 is a similar, very good guideline for maintaining and protecting the integrity of electronic records. Like Part 11, it should not be feared as its requirements may already be met by the healthcare industry in using standard best practices and best software practices in order to keep patients safe.

Much like Part 11, Annex 11 is not a passive guidance. Annex 11 requires that both technical and procedural solutions for a system should fully meet the spirit of the guidance or law in EU countries where it may now be on their statute books.

3.3 ICH GCP

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a set of guidelines that brings together the regulatory principles of Europe, Japan and the United States that applies to the scientific and technical aspects of Investigational product trials and registration.

The purpose of ICH is to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or do away with the need to duplicate the testing carried out during the research and development of new medicines. The applied principles of ICH are known as 'Good Clinical Practice' or GCP.

The introduction to ICH GCP explains its scope and purpose quite clearly;

> "Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.
>
> The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions…
>
> This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects."

ICH GCP, when practically applied on systems (e.g. Functional and procedural controls, audit trails, system use, and use training), should largely be met by the application of the requirements as described in Part 11 and Annex 11. Therefore, ICH GCP principles

should not be feared by the healthcare industry and is most likely already being met by EHR systems that follow best practices in order to keep patients safe.

3.4 Patient Privacy Laws

Healthcare sites are very familiar with patient privacy laws such as HIPAA (Health Insurance Portability and Accountability Act) in the US, the European Commission Data Protection Directives (95/26/EC and 2002/58/EC), and other individual country protection laws. These regulations apply to clinical research data as well, and since most healthcare sites are already bound by these laws, we will not go into detail regarding them in this paper.

3.5 FDA Guidance for Industry: Computerized Systems Used in Clinical Investigations

Another major, relevant document is the US FDA's Guidance for Industry: Computerized Systems Used in Clinical Investigations (CSUCI) published in May 2007. This document is intended to be a companion to Part 11. As noted in the document:

> "FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited."

3.6 eSource Guidance Papers

The EU eSource paper, from GCP Inspection Services Group of EMEA, was put out for comment on March 2008 and has not yet been made final. The paper sought to layout a clear set of requirements for the use and acceptance of electronic source documents and data. The authors understood and made clear that further clarification will be needed on the requirements as well as the relationship to the ICH GCP defined roles and responsibilities in clinical trials. EMEA tried to harmonize their thinking on the subject by taking their considered twelve requirements from the Clinical Data Interchange Standards Consortium (CDISC) eSource paper, "Leveraging the CDISC Standards to facilitate the use of Electronic Source Data within Clinical Trials.[4]", issued in November, 2006. The relevance of the CDISC paper to this document is in regard to electronic source data (eSource). As the CDISC paper states:

> "One class of data in particular, source data, has caused particular concern within the industry. Whereas in the traditional world, data were recorded on the tangible and comfort-giving piece of paper, now the same data are stored electronically, allowing the information to be quickly copied, transferred, changed or deleted. Therefore, the industry

[4] This paper can be found on the CDISC website: www.cdisc.org.

must consider how the potential benefits of electronic source can be realized, while minimizing the risks and impact on current practices and personnel that it brings."

Contained within the CDISC paper are 12 requirements for source data, regardless of the medium (e.g., paper, electronic) in which they are held (see Appendix 3). These requirements are derived from the regulations mentioned above and important to users of EHR systems if the system will store the source data for clinical research. *Please note that the CDISC paper discusses requirements for source data regardless of the medium used to collect and store them, whereas the EHRCR User Requirements document discusses requirements specifically for computerized EHRs used in clinical research.*

4 Benefits of Using an EHR Product Certified for Clinical Research

The HL7 EHRCR Functional Profile details the functional requirements for an EHR system that would also have the functionality to enable clinical research source records to be collected and maintained. Now that this profile has been accepted as an HL7 standard through stakeholder balloting, we are looking to include certification of EHR systems for clinical research into certification processes from the US Certification Commission for Healthcare Information Technology (CCHIT) and the EU EuroRec.

Creation of a process for certification of EHR systems against these requirements would provide benefits for sites, sponsors, and EHR vendors by:

- Clearly differentiating system-supported requirements from requirements that must be met through site processes
- Providing a "blueprint" to help guide the development efforts of the EHR vendors, and their customers' system selection and process development activities
- Consolidating a significant portion of the system assessment efforts into one certification as opposed to multiple audits by individual sponsors. The process will still need to be assessed, but should become more straightforward.

Even before certification of EHR systems for clinical research is available, the EHRCR Functional Profile is a valuable tool for sponsors, sites and vendors to use to prepare themselves for these activities.

The ability to leverage sites' EHR systems to capture and transfer clinical trial data will result in numerous practical benefits for both sites and sponsors:

- Increased comfort level for the sponsor resulting from compliance with clinical research regulations
- Minimized data transcription resulting in increased efficiency, improved data quality, a reduced administrative burden for the site research personnel, and the ability for site monitors to shift monitoring activities from source data verification to clinical activities.

- Enhanced patient safety resulting from the increased transparency between research and healthcare.

For future EHRCR Functional Profile releases, we anticipate adding additional benefits:

- User-friendly workflows facilitated by the integration of research into the healthcare workflow, allowing site research personnel to use the same user interface for healthcare and research activities.
- Decreased requirements for technology-related site training enabling streamlined site initiation and study start-up.

Thus, a site that chooses a certified EHR system can be assured that the system has the functionality to meet regulations for storing clinical research source data. Choosing to follow the guidance given in this paper regarding system implementation and use can ensure an interoperable environment for EHR-based clinical research. Such an environment can open up additional opportunities for data re-purposing to support clinical research, such as prospective clinical trials, retrospective studies, and safety reporting.

5 Addressing Compliance at the Investigative Site

Historically, clinical research and health care have taken separate paths in developing electronic solutions to support their needs. Now we see a strong need to connect these separate silos. In this paper, we try to address the regulatory aspect of connecting two electronic worlds. If you are thinking about using your existing EHR system to document eSource for clinical research studies, you may be able to use EHR system functionality combined with site processes to meet the expectations of regulated clinical research. This section will demonstrate how this might be accomplished.

5.1 Risk Assessment / Analysis

There are many ways to meet the expectations of regulatory agencies regarding these regulations. One could take a risk-based approach to help identify the areas of the EHR system that are most critical to clinical research. In this way, efforts in following clinical research regulations will be focused, and not affect areas of the EHR system that do not apply to clinical research (such as functions that handle reporting to insurance companies). A risk assessment uses available information to predict the likelihood of an event occurring and the magnitude of the consequences; a basic risk assessment template is provided in Appendix 4.

To create a risk assessment plan, first have a clear understanding of the records generated and how they are used. Not all computer systems have to comply with regulations but certain ones do. Ask yourself if your system (or portions of your system) meet the following conditions:

- Used to create, modify, maintain, or transmit electronic record(s) that are required to demonstrate compliance with regulations (predicate rule and/or statutory requirements) (e.g., medical records, adverse event tracking/reporting, protocol required assessments/documentation, drug accountability records, records relating to the transfer or archiving of regulated records, etc.)
- Used to make decisions impacting patient safety and/or the conduct or assessment of a clinical trial
- Used to produce information for a regulatory inspection (e.g., training records, SOPs, change control records, etc.)

If you answer yes to any of these points, include the system in your risk assessment plan. See Appendix 4 for a sample risk assessment template.

5.2 Practical Considerations for Requirements of an EHR for Clinical Research

The table below shows the base User Requirements of an EHR system if data from the system is to be used as source for clinical research. These base User Requirements satisfy regulations and guidance that pertain to clinical research. Also included are some user requirements that are necessary to support the entire EHRCR Core vision (such as a minimum set of required data elements).

We have added a column describing how each of these requirements could be met by the users of these systems if not met by the system itself. We have also tried to briefly describe the importance of these requirements, so that the users can determine for themselves the risks involved if their system does not meet the requirements, or how they might fulfill them outside the system.

When certification of EHR systems for clinical research becomes a reality (via CCHIT and EuroRec certifications), an EHR vendor could have their product certified and a buyer will know that these requirements are met. We anticipate the EHRCR Functional Profile will be the basis for these certifications. Prior to a certification stamp on a vendor's product, the EHRCR Functional Profile can be used by research sponsors, investigational site staff, or EHR vendors to determine how suitable a particular system is for clinical research. A mock assessment that this team performed on one major EHR vendor system, indicated that this system was currently almost 95% compliant with the EHRCR Functional Profile. This is very encouraging, and we expect that other vendor solutions are equally prepared to take on the responsibility of providing source data for clinical research.

The user requirements are divided into two categories: System and Process. Any EHR system that is compliant to the EHRCR Functional Profile will satisfy all the system requirements. Some of the process requirements may be satisfied by system features but can also be satisfied procedurally. Other process requirements pertain not to the system itself, but to how the system is used at the site and these requirements can never be part of a system certification but must always be addressed by the investigative site.

5.2.1 Checklist for using your EHR system as a source for clinical data

Investigator site responsibility with respect to system installation and maintenance may be handled by their organization's IT department or a vendor. In these cases, the investigational site is still responsible for ensuring that these other parties are fulfilling these responsibilities. To see the exact mapping between the EHRCR User Requirements and the sections of the clinical research regulations and guidances they are based on, refer to the EHRCR User Requirements Addendum (see reference section).

Base User Requirements for EHR systems that will provide source data for clinical research	**Regulation / Guidance based on**	**Site responsibilities for meeting these requirements**	**Does your site (system + processes) meet this requirement? (Y/N)**
System Requirements		***All system requirements must be satisfied by the EHR system. Investigator site must ensure that their EHR system is compliant.*** *Once EHRCR Certification of vendor systems is possible, then a certification seal will provide assurance that the functionality of the system is compliant*	
The system can capture a minimum set of **Demographic and Patient Characteristics** data.	CDISC CDASH highly recommended data elements	System needs to be able to accept entry of all data elements. Site personnel are responsible for ensuring complete documentation of all data required for research. Site needs to understand research protocol requirements, how and where this information is stored in their system and how this will be transferred to sponsor.	
The system can capture a minimum set of **Adverse Event** (problem) data.	CDISC CDASH highly recommended data elements		
The system can capture a minimum set of **Patient History** data.	CDISC CDASH highly recommended data elements		
The system can capture a minimum set of **Medication/Therapy** data.	CDISC CDASH highly recommended data elements		
The system can capture a minimum set of **Physical Exam** data.	CDISC CDASH highly recommended data elements		

Base User Requirements for EHR systems that will provide source data for clinical research	Regulation / Guidance based on	Site responsibilities for meeting these requirements	Does your site (system + processes) meet this requirement? (Y/N)
The system can capture a minimum set of **Vital Signs** data.	CDISC CDASH highly recommended data elements		
The system can capture a minimum set of **Common Identifier Variables** and **Common Timing Variables**.	CDISC CDASH highly recommended data elements ICH GCP		
System has the ability to store and retrieve records in a way that is attributable to a patient	21 CFR Part 312 CSUCI EU Directive 2008 28 ICH GCP		
System has the ability to produce a human-readable copy of data (which includes associated audit trails and translation of any coded data)	CSUCI Part 11 EU Annex 11 EU Directive 2008 28		
Specified de-identified data can be extracted for clinical research.	HIPAA ICH GCP EU Directive 2008 28	Sites should take caution such that no information that could identify a patient may be shared with the sponsor (via electronic means or manually).	
The system presents an overview of all patient consents and/or authorizations.	HIPAA 21 CFR Part 312 EU Directive 2001 20	This does not mean that the Informed Consent form itself must be electronic and electronically signed, only that the system can track if and when a patient has signed the form.	
System will have an audit trail to include recording date/time/author of any data creation, change, or deletion	CSUCI Part 11 EU Annex 11 ICH GCP	Site must ensure that audit trail functionality has been installed and is turned on	
System will not allow new audit trail information to over-write existing (previous) information	CSUCI Part 11 ICH GCP		
There will be sufficient system and/or process	CSUCI	This may be handled via the site operating	

Base User Requirements for EHR systems that will provide source data for clinical research	Regulation / Guidance based on	Site responsibilities for meeting these requirements	Does your site (system + processes) meet this requirement? (Y/N)
controls for backup and recovery procedures	EU Annex 11 ICH GCP	system and associated procedures or via the EHR system. The site is responsible for ensuring the backup and recovery method is working and documented.	
System will limit the number of log-in attempts and record unauthorized access log-in attempts.	CSUCI EU Annex 11	This may be handled via the site operating system and associated procedures or via the EHR system. Site must ensure that this feature is installed and turned on.	
System will allow and enforce password or other access keys to be changed at established intervals.	CSUCI EU Annex 11	Site must ensure that this feature is installed and turned on. The site is responsible for establishing reasonable intervals.	
System feature to allow automatic logoff or other data lock (such as password protected screen saver) after a set period of time of inactivity	CSUCI EU Annex 11	Site must ensure that this feature is installed and turned on. However, if your system does not have an automatic logoff, then the users should all have password-protected screen savers (a feature of the operating system software) in use. Users should not have the ability to turn off the password-protected screen saver functionality if it is used instead of automatic logoff from the system.	
Controls exist to ensure system date and time are correct (e.g. system clock synchronizes to a date and time provided by international standard setting agency).	CSUCI	This may be handled via the site operating system and associated procedures or via the EHR system. The site is responsible for ensuring the method employed is working and documented.	
The system has the ability to create, maintain and apply the roles, access permissions and capabilities of each user that accesses the system, such that users have access only to those system features and functions to which they have been granted access.	CSUCI Part 11 EU Annex 11	Sites must ensure that accounts are configured so that users have access to only those features that they should have access to (often referred to as roles). Also, there should be an administrator to grant accounts to users upon justification of their need for an account. If you are using a hosted	

Base User Requirements for EHR systems that will provide source data for clinical research	Regulation / Guidance based on	Site responsibilities for meeting these requirements	Does your site (system + processes) meet this requirement? (Y/N)
		system, be sure that the vendor will provide the user administration and that you understand the process for obtaining and removing accounts.	
Controls exist such that the ability to change system date or time is limited to authorized personnel and such personnel should be notified if a system date change is detected.	CSUCI	This may be handled via the site operating system and associated procedures or via a hosting vendor. The site is responsible for ensuring the method employed is working.	
System will allow audit trail to utilize standard time-keeping method such that the local time can be derived.	CSUCI	This is necessary if access to a central system is distributed across time zones. The time on the individual client PCs accessing the central system could be different from the time on the central system.	
Process User Requirements			
Process and/or system controls must ensure data used for clinical research source records are retained for the legal period.	CSUCI Part 11 EU Annex 11 EU Directive 2008 28 ICH GCP	Sites are responsible for knowing the legal retention period and for ensuring that methods employed to meet this requirement are working.	
There will be sufficient system and/or process controls to prevent or mitigate effects of viruses, worms, or other harmful software code	CSUCI EU Annex 11	This may be handled via the site operating system and associated procedures. The site is responsible for ensuring the method employed is working and documented.	
There will be sufficient process control for the system covering Disaster Recovery Procedures / Contingency Planning	CSUCI EU Annex 11 ICH GCP	The group responsible for providing backups, recovery plans in case of disaster and contingency plans for the EHR software/hardware, whether it is your IT department or a vendor, should have an SOP describing how these will be handled. You should have access to this SOP.	
The site will have documented procedures for maintaining a copy of the source data at another location other than the clinical site	CSUCI EU Annex 11		
The site will have documented procedures for	CSUCI	This includes the description and specific use	

Base User Requirements for EHR systems that will provide source data for clinical research	Regulation / Guidance based on	Site responsibilities for meeting these requirements	Does your site (system + processes) meet this requirement? (Y/N)
controlling user process at the site (system security measures, how source data are obtained and managed, what electronic systems are used)	Part 11 EU Annex 11 ICH GCP	of software, hardware, and physical environment and the relationship. If your site has an IT dept. which installs your EHR system, they should have such an SOP available. If you use an ASP model, the vendor supplying this should have this SOP and make it accessible to you in case of an audit.	
There will be a process to demonstrate that individuals who develop, maintain, or use the system have appropriate education, training, and experience necessary to perform their assigned task.	CSUCI Part 11 ICH GCP	Those using the system must have the training necessary to be able to accomplish their assigned tasks. This training should be documented and the records available at your site	
There will be a vendor process to demonstrate that development and modifications of the system and system documentation use good software development lifecycle practices including documented system validation and change control such that the integrity of the data is maintained when changes are made to the system and/or documentation, such as software upgrades, security and performance patches, equipment or component replacement.	CSUCI Part 11 EU Annex 11	An audit of the vendor must be performed to determine if this requirement is met. While this requirement is not part of the EHRCR functional profile as it is not part of the functions of a system, it is possible that a future system certification (through CCHIT or EuroRec) could ensure this.	
There will be an investigator *site* process to demonstrate that any changes to the system are documented and any required system validation and change control is performed such that the integrity of the data is maintained when changes are made to the computerized system, such as software upgrades, security and performance patches, equipment or component replacement	CSUCI Part 11 EU Annex 11 ICH GCP	When purchasing or upgrading software, it is typical to have a list of requirements for what it should do and then test to see that it does perform those functions. Validation is a formalization of this process and good business practice. Validation is only required for the parts of the system (modules) that meet the requirements in section 3.A.	
There will be a system function and/or process to	CSUCI	There should be a list of all those who have	

Base User Requirements for EHR systems that will provide source data for clinical research	Regulation / Guidance based on	Site responsibilities for meeting these requirements	Does your site (system + processes) meet this requirement? (Y/N)
ensure the ability of the site to provide a cumulative directory of all personnel who use or access the data for the trial.	ICH GCP	access to the EHR and what functions (e.g., browse only, update data) they can perform. You should know who maintains this list (e.g., IT dept., your office) and it should be easily accessible in the case an audit occurs. Typically, whoever provides the access accounts would have such a list of users.	
Measures must be in place such that persons who create, modify, or delete patient records should not be able to modify the audit trail or the system clock	CSUCI	This cannot be ensured by system functionality. The site must make sure that the same people are not allowed to enter data as are allowed to change system clock etc.	

APPENDIX 1: Glossary

ALCOA	Attributable, Legible, Contemporaneous, Original and Authentic – keys to trustworthy data
ASP	Application Service Provider – vendor of a system might offer to host that system for your use.
CCHIT	Certification Commission for Healthcare Information Technology (US)
CDASH	CDISC standard: Clinical Data Acquisition Standards Harmonization
CDISC	Clinical Data Interchange Standards Consortium
Certification	A quality labeling process provided by an independent, unbiased, professional and trustworthy organization that will indicate that a system has met a specific set of criterion.
Certified Copy	(From US FDA Guidance for Industry: Computerized Systems Used in Clinical Investigations) A certified copy is a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.
Clinical trial	Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.
CSUCI	Computerized Systems Used in Clinical Investigations (FDA Guidance)
EDC	Electronic Data Capture (system used for entering clinical research data at investigator sites)
EHR	Electronic health record
EHRCR FP	Functional profile for describing functionality needed to conduct clinical research via an EHR system
EuroRec	European Institute for Health Records (network of National ProRec centres throughout Europe to promote adoption of electronic healthcare records. ProRec centres provide certification of EHR systems.)
FDA	Food and Drug Administration (US governmental agency)
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HL7	Health Level Seven Standards Organization
ICH	International Committee on Harmonization
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IT	Information Technology
Q-REC	European Quality Labeling and Certification of Electronic Health Record Systems
Research Protocol	(Also called Clinical Trial Protocol) A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guidance, the term protocol refers to protocol and protocol amendments.
SDLS	System Development Life Cycle
SOP	Standard Operating Procedure
Sponsor	Clinical research sponsor (e.g. bio-pharmaceutical company)

APPENDIX 2: References

1. Privacy Laws
   - 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 (2004). http://www.hipaadvisory.com/regs/finalprivacy/
   - European Commission: Justice and Home Affairs: Data Protection http://ec.europa.eu/justice_home/fsj/privacy/index_en.htm
     - Directive 95/46/EC on the protection of individuals with regard to the processing of personal data to protect fundamental rights and freedoms, notably the right to privacy and on the free movement of such data.
     - Directive 2002/58/EC of the European Parliament and of the Council of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications)

2. Regulations
   - U.S. FDA 21 CFR Part 11 Electronic Records; Electronic Signatures Final Rule (1997), http://www.fda.gov/ora/compliance_ref/part11/FRs/background/pt11finr.pdf
   - U.S. FDA 21 CFR Part 312 Investigational New Drug Application (Revised April, 2006), also Parts 50, 54, 56, 314, and 812
   - EU Directive 2001/20
   - EU Directive 2008/28
   - EU Annex 11

3. Guidance
   - U.S. FDA Guidance for Industry, Computerized Systems Used In Clinical Investigations (CSUCI) (May 2007); http://www.fda.gov/cder/guidance/7359fnl.pdf
   - U.S. FDA, Guidance for Industry, Part 11, Electronic Records; Electronic Signatures - Scope and Application (2003). http://www.fda.gov/cder/guidance/5667fnl.htm
   - ICH (International Conference on Harmonization), FDA, E6 Good Clinical Practice: Consolidated Guidance", (1996). http://www.fda.gov/cder/guidance/959fnl.pdf
   -

4. Standards Development Organizations
   - 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

5. EHR Certifying Bodies
   - CCHIT – Certification Commission for Healthcare Information Technology: http://www.cchit.org
   - EuroRec – European Institute for Health Records (EuroRec): http://www.eurorec.org/

     http://www.eurorec.org/projects/qrec.cfm?actief=q-rec
6. Other References
   - CDISC eSDI, Leveraging the CDISC Standards to Facilitate the use of Electronic Source Data within Clinical Trials, (2006), http://www.cdisc.org/eSDI/eSDI.pdf
   - Embi, PJ, Jain, A, Clark, J, Bizjack, S, Hornung, R. Harris, M, "Effect of a Clinical Trial Alert System on Physician Participation in Trial Recruitment", Archives of Internal Medicine VOL 165, OCT 24, 2005
   - AllScripts case study, located at http://www.allscripts.com/siteresources/files/casestudies/TheEHRSolutiontoClinicalTrial_HolstonCaseStudy.pdf;
   - GPRD – General Practitioners Research Database - http://www.gprd.com/intro/default.asp
   - National Committee on Vital and Health Statistics, Enhanced Protections for Uses of Health Data: A Stewardship Framework for "Secondary Uses" of Electronically Collected and Transmitted Health Data (Oct, 2007), http://www.ncvhs.hhs.gov/071031lt.pdf

APPENDIX 3: CDISC requirements for source data in any medium[5]

Requirement 1:	An instrument used to capture source data shall ensure that the data are captured as specified within the protocol.
Requirement 2:	Source data shall be Accurate, Legible, Contemporaneous, Original, Attributable, Complete and Consistent.
Requirement 3:	An audit trail shall be maintained as part of the source documents for the original creation and subsequent modification of all source data.
Requirement 4:	The storage of source documents shall provide for their ready retrieval.
Requirement 5:	The investigator shall maintain the original source document or a certified copy.
Requirement 6:	Source data shall only be modified with the knowledge or approval of the investigator.
Requirement 7:	Source documents and data shall be protected from destruction.
Requirement 8:	The source document shall allow for accurate copies to be made.
Requirement 9:	Source documents shall be protected against unauthorized access.
Requirement 10:	The sponsor shall not have exclusive control of a source document.
Requirement 11:	The location of source documents and the associated source data shall be clearly identified at all points within the capture process.
Requirement 12:	When source data are copied, the process used shall ensure that the copy is an exact copy preserving all of the data and metadata of the original.

[5] CDISC eSDI, Leveraging the CDISC Standards to Facilitate the use of Electronic Source Data within Clinical Trials, (2006), http://www.cdisc.org/eSDI/eSDI.pdf

APPENDIX 4: Sample Risk Assessment Template

A. Risk Identification

Identify the types of risk that could arise from the activity, such as:

Reduced Patient Safety

Financial loss

Inadvertent or deliberate breach of legislation, policy, or ethical standards

Legal liability

Other

B. Risk Quantification

Any risks identified should be quantified in terms of likelihood and possible consequences.

Qualitative measures of likelihood*

Level	Descriptor	Example detail description
1	Rare	May occur only in exceptional circumstances
2	Unlikely	Could occur at some time
3	Possible	Might occur at some time
4	Likely	Will probably occur in most circumstances
5	Almost certain	Is expected to occur in most circumstances

Qualitative measures of consequence/ impact*

Level	Descriptor	Example detail description
1	Insignificant	Low financial loss
2	Minor	Medium financial loss
3	Moderate	High financial loss
4	Major	Major financial loss
5	Catastrophic	Huge financial loss

Qualitative risk analysis matrix – level of risk*

Likelihood	*Consequences*				
	1 Insignificant	2 Minor	3 Moderate	4 Major	5 Catastrophic
1 (Rare)	Low	Low	Medium	High	High
2 (Unlikely)	Low	Low	Medium	High	Extreme
3 (Moderate)	Low	Medium	High	Extreme	Extreme
4 (Likely)	Medium	High	High	Extreme	Extreme
5 (Almost certain)	High	High	Extreme	Extreme	Extreme

C. Risk Treatment

Outline strategies to reduce likelihood and/or consequences of identified risk

- The risk level indicates what level of susceptibility may exist toward patient safety, legal ramifications, financial loss, etc. should something go wrong with a system. Based on this indication, recommendations will be made on how to control this risk such that the system as put into production *poses only an acceptable and known risk in this area*

For more information on the project or the EHRCR Functional Profile:
www.ehrcr.org
www.eclinicalforum.com