

# **Practical Considerations for Clinical Trial Sites using Electronic Health Records (EHRs) Certified for Clinical Research**

## **Addressing Regulatory Considerations**

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Sponsored by eClinical Forum  
[www.ehrer.org](http://www.ehrer.org)

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## 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).

The EHRCR project team (initially a collaborative effort of eClinical Forum and PhRMA along with HL7 and EuroRec) has produced a number of deliverables<sup>1</sup> including

- ***User Requirements document*** outlining the project vision of fully integrated healthcare (eHealth) and research (eResearch) systems as well as clearly showing the minimum Regulatory-mandated clinical research requirements that must be met in order to use electronic data from electronic health records as source for clinical research.
- ***EHRCR Functional Profile (approved by HL7, ANSI, and EuroRec, and under joint consideration by CEN and ISO)*** delineates the high-level requirements necessary, based on the User Requirements (above) and the succinct criteria that can be used to evaluate EHR systems for use with clinical research.

The EHRCR Functional Profile aims to provide practitioners, research community and regulators with a level of confidence that the integrity of clinical research data is protected, source data are stored in a manner compliant with clinical research regulations and process redundancy is minimized. The profile (a) is founded on current clinical research regulations / guidances (b) translates requirements into measurable criteria to assess suitability of a system for clinical research, and (c) was used as a input for the ***CCHIT Certified® 2011 Clinical Research certification option for Ambulatory EHRs.***

There are two voluntary certification programs for EHR systems in the US. They provide a first step towards having some consistency in EHR systems in various institutions where clinical research is being performed, however this certification is directed towards healthcare and does not include regulatory requirements for clinical research.

- **CCHIT Certified® EHR certification** by the nonprofit Certification Commission for Health Information Technology (CCHIT®), is an independently developed, rigorous inspection of integrated EHR functionality, interoperability, and security. As part of the process, successful use is verified at live sites and product usability is rated. It is intended to serve providers looking for greater assurance that a product will meet their needs. Many CCHIT Certified products are also certified in the federal government's EHR certification program, called the Office of the National Coordinator Authorized Testing and Certification Body (ONC-ATCB) program for 2011/2012. CCHIT is an ONC-ATCB.

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<sup>1</sup> These documents can all be found at [www.ehrcr.org](http://www.ehrcr.org).

- **ONC-ATCB certification** inspection is limited to Department of Health and Human Services (HHS) criteria and standards establishing a minimum floor for EHR technology. Providers are responsible for assuring that they possess certified EHR technology meeting all of the requirements. No site verification or usability testing is done under this program. Institutions and providers using ONC-ATCB certified EHR technology are eligible for government incentives if they meet “Meaningful Use” objectives defined by the Centers for Medicare and Medicaid Services (CMS). This certification program is being rolled out in three stages (2011 through 2016) with incremental criteria for EHR testing and certification, and Meaningful Use objectives for providers.

In June 2011, CCHIT released a certification for Clinical Research that can be applied to any EHR system that already possesses a system-level CCHIT Certified 2011 Ambulatory EHR certification (first bullet above). This is the first system-level certification of EHRs in the Clinical Research arena, however this certification applies only to the system and not its installation and use at a particular site. It therefore becomes apparent that certification of EHR systems for clinical research is not sufficient alone to provide proof of a compliant environment for clinical research. Research sites will need to implement and use such systems in a manner that complies with the regulations and guidances.

## I. Purpose of this guide

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

- Understanding and complying with regulations when participating in clinical research
- Selecting or upgrading an EHR system to hold data which could potentially become source data to support regulations applicable to 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
- Clearly differentiating system-supported requirements from requirements that must be met through site processes

An Implementation checklist is provided for use by research sites when selecting and implementing EHR software, or to evaluate whether existing software is suitable to provide source data for clinical research.

## II. Why should this information be important to you?

This document provides a practical context for the regulatory requirements and guidances (US and EU) governing clinical research records, systems & processes. The same responsibilities of the investigator to ensure that the source data are accurate, attributable, legible, contemporaneous, and original, exist whether those data are hand-written on

paper or entered and stored electronically. Additionally, if data are entered and stored into an Electronic Health Record (EHR) system as the sole source and used in regulated clinical research, that system must be compliant with these clinical research regulations. For example, data in EHR systems that are used 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. Many of these requirements are also required of healthcare systems and/or otherwise considered good system practices.

Regulatory documents relevant to clinical research data handling include the following. For a discussion on each regulation/guidance and its relevance to healthcare systems, please see Appendix 2.

#### Regulations and Directives

- FDA 21 CFR Part 11, Electronic Records; Electronic Signatures Final Rule
- FDA 21 CFR Part 312, Investigational New Drug Application
- EU Annex 11 (30-June-2011)
- EU Directive 2001/20
- EU Directive 2005/28
- EU Directive 95/46/EC (Data Protection)
- EU Directive 75/318/EEC (July 1990)
- US DHHS Health Insurance Portability and Accountability Act (patient & data privacy 45 CFR 160, 162, 164 ) (HIPAA)

#### Guidances and Reflection Papers :

- ICH E 6 Good Clinical Practice: consolidated guideline (1996) (GCP)
- FDA Guidance: Computerized Systems Used in Clinical Investigations (CSUCI (May 2007)
- FDA Guidance for industry Part 11, Electronic Records; Electronic Signatures- Scope and Application (August 2003)
- EMA Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical research (1-Aug-2010)

### **III. Benefits of Using an EHR Product, Certified for Clinical Research**

Considering new regulatory guidances in both the EU and US (see discussion, Appendix 2), requiring clinical research sponsors to assess electronic health records that hold the first capture of data to be used in clinical research, it is even more critical now that there

is a process for the certification of EHR systems which meet clinical research requirements.

Such a certification would provide benefits for sites, sponsors, and EHR vendors by:

- Providing a "blueprint" to help guide the development efforts of the EHR vendors to build a clinical research compliant system
- Aiding EHR customers' in system selection
- Consolidating a significant portion of the system assessment efforts into one certification as opposed to multiple audits by individual sponsors.
- Increased comfort level for the sponsor resulting from compliance with clinical research regulations thus enabling:
  - 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.

A site that chooses an EHR system certified for CR 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 a reliable and secure 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.

Currently there are no systems in the US or EU that are certified for clinical research, however CCHIT released a certification qualification program for Clinical Research in June 2011. Certifications for healthcare use (such as ONC-ATCB certification supporting Meaningful Use in the US) can be a base upon which additional clinical research criteria can be evaluated (see table in section V.B). As an alternative, the EHRCR Functional Profiles, either in the ANSI-approved HL7 version or the EuroRec approved version, can provide both Implementation Specifications and Conformance Criteria for evaluating these systems.

#### **IV. Integrating Healthcare Enterprises (IHE)**

We recognize that electronic healthcare is typically comprised of a variety of different systems. Healthcare professionals seeking to acquire or upgrade systems need a reliable way to specify a level of compliance to standards sufficient to achieve efficient interoperability. The purpose of the IHE initiative is to meet that need. While it does not specifically address integrating with clinical research systems, the concepts provided will apply. The following text has been taken from the IHE website.

IHE Profiles provide a common language for purchasers and vendors to discuss the integration needs of healthcare sites and the integration capabilities of healthcare IT products. They offer developers a clear implementation path for communication standards supported by industry partners which are carefully documented, reviewed and tested. They give purchasers a tool that reduces the complexity, cost and anxiety of implementing interoperable systems.

#### Profiles and Standards

IHE Profiles organize and leverage the integration capabilities that can be achieved by coordinated implementation of communication standards, such as DICOM, HL7 W3C and security standards. They provide precise definitions of how standards can be implemented to meet specific clinical needs.

IT Infrastructure Domain Profile: Retrieve Form for Data Capture (RFD) enables EHR applications to directly request forms from clinical trial sponsors and public health reporting and populate those forms with data from the EHRs. The profile also provides a mechanism to archive data.

## **V. Addressing Compliance at the Investigative Site**

This section will guide you in how to use EHR system functionality combined with site processes to meet the expectations of regulated clinical research. .

### ***A. Risk Assessment / Analysis***

There are many ways to meet the expectations of regulatory agencies regarding these regulations. For complex systems like EHRs, it is expected and acceptable to take a risk-based approach to help identify the areas of the EHR system that are most critical to clinical research. In this way, compliance with clinical research regulations will be focused on the critical components or modules of the EHR system (and their associated functions and process steps). Those modules and functionalities that do not apply to clinical research (such as reporting to insurance companies or signatures documenting approvals of nonclinical research-related process steps) will not be affected and need not be assessed.

## ***B. 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. ***Sites are encouraged to use this checklist to determine if they are ready for sourcing regulated clinical research in their EHR system.***

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.

**Key Point:** If your system has been “certified”, such as ONC-ATCB 2011/2012<sup>2</sup> (US) or the CCHIT Certified 2011 Ambulatory EHR (US) or CCHIT Certified 2011 Ambulatory EHR + Clinical Research (US), then it may meet many of the requirements shown below, and the checklist will indicate which additional criteria need to be handled by the investigative site. In the case where the existing certification does not fully meet the clinical research user requirement (as indicated below), it is recommended to assess against the EHRCR criteria (ANSI approved) as shown in the EHRCR User Requirements document Section 6.1.2.<sup>3</sup>

Regardless of whether an EHR system meets the system requirements shown below, it is still up to the investigative site to ensure that the system has been installed properly and all the necessary features are turned on and proper procedures are being followed at the site. ***Each clinical research site should use the following checklist to ascertain the readiness of their system for clinical research and to guide them toward processes that will facilitate compliance with the clinical research regulations.***

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<sup>2</sup> The EHRCR Project team reviewed FDA 45 CFR Part 170, Health Information Technology Standards, Implementation Specifications, and Certification Criteria and Certification Programs for HIT (commonly referred to as “Meaningful Use”) and determined that while it is a good basis for healthcare, it is not sufficient for clinical research. However, 45 Part 170 does not conflict with any clinical research regulations or guidances.

<sup>3</sup> EHRCR User Requirements document is available on [www.ehrcr.org](http://www.ehrcr.org).

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

<b>Base User Requirements (UR) for EHR systems that will provide source data for clinical research</b>	<b>Applicable Regulation / Guidance / Reference</b>	<b>UR is met by certification criteria</b>	<b>Site responsibilities for meeting these requirements</b>	<b>Does your site (system + processes) meet this requirement? (Y/N)</b>
<p><i>Minimal set of EHR system and Inv site requirements needed to use electronic source from an EHR system in regulated clinical research. Process requirements may be satisfied by system features and/or procedurally. Some process requirements pertain not to the system itself, but to how the system is used at the site. These requirements can never be part of a system certification but must always be addressed by the research site.</i></p>	<p><i>Includes govt regulations &amp; guidances, &amp; some industry standards for data collection providing a minimal set of data that make the effort of collecting CR data in an EHR system worthwhile. To see the exact mapping between the User Requirements and the clinical research regulations and</i></p>	<p><i>If a system is certified for Clinical Research via the HL7-ANSI EHRCR Functional Profile, or the EuroRec EHRCR Functional Profile then all of these User Requirements will be met and the system will be suitable to provide source data for clinical research. This column indicates if other certifications meet the needs of clinical research.</i></p> <p><i>The following codes indicate:  A – met by CCHIT Ambulatory  A+CR – met by CCHIT Ambulatory plus CCHIT CR  MU – met by US “Meaningful Use” ONC-ATCB 2011/2012 Certification</i></p> <p><i>Key Point: a code in this</i></p>	<p><i>Indicates what a site must do to ensure that this requirement is met by their implementation of the EHR system.</i></p>	

	<i>guidances, refer to the EHRCR User Reqs Doc.</i>	<i>column means that the certified system itself is capable of complying, however each site must implement the system in such a way that this feature is permanently turned on.</i>		
<b>System Requirements</b>				
EHRCR-T0-DA.100 The system can capture a minimum set of <b>Demographic and Patient Characteristics</b> data.	CDISC CDASH highly recommended data elements	A MU	The value of storing clinical research data in EHR System is so that it is available with all other data required for clinical care. Storing the data as CDISC CDASH discrete elements greatly increases the ease with which these data can be used with any clinical research sponsor as needed. The EMA reflection paper re-enforces the ICH E6 (R1) GCP concept that "An instrument used to capture source data should ensure that the data are captured as specified in the protocol." The CDISC CDASH elements can help ensure consistency across protocols as well CDISC CDASH is not a regulated requirement, however is highly recommended.	
EHRCR-T0-DA.110 The system can capture a minimum set of <b>Adverse Event</b> (problem) data.	CDISC CDASH highly recommended data elements	A MU		
EHRCR-T0-DA.120 The system can capture a minimum set of <b>Patient History</b> data.	CDISC CDASH highly recommended data elements	A MU		
EHRCR-T0-DA.130 The system can capture a minimum set of <b>Medication/Therapy</b> data.	CDISC CDASH highly recommended data elements	A MU		
EHRCR-T0-DA.140 The system can capture a minimum set of <b>Physical Exam</b> data.	CDISC CDASH highly recommended data elements	A		
EHRCR-T0-DA.150 The system can capture a minimum set of <b>Vital Signs</b> data.	CDISC CDASH highly recommended data elements	A MU		
EHRCR-T0-DA.160 The system can capture a minimum set of <b>Common Identifier Variables</b> and <b>Common Timing Variables</b> .	CDISC CDASH highly recommended data elements ICH GCP	A		

EHRCR-T0-IO.200 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 2005 28 ICH GCP	A+CR MU		
EHRCR-T0-IO.210 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 2005 28	A+CR MU		
EHRCR-T0-IO.220 Specified de-identified data can be extracted for clinical research.	HIPAA ICH GCP EU Directive 2005 28	A+CR	Sites should take caution such that no information that could identify a patient may be shared with the sponsor (via electronic means or manually).	
EHRCR-T0-IO.230 The system presents an overview of all patient consents and/or authorizations.	HIPAA 21 CFR Part 312 EU Directive 2001 20	A MU	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.	
EHRCR-T0-DS.300 System has an audit trail to include recording date/time/author of any data creation, change, or deletion	CSUCI Part 11 EU Annex 11 ICH GCP EMA	A MU	Site must ensure that audit trail functionality has been installed and is working correctly.	
EHRCR-T0-DS.310 System does not allow new audit trail information to overwrite existing (previous) information	CSUCI Part 11 ICH GCP	A MU requires the system can <i>detect</i> the alteration of audit logs. Further system functionality is required to <i>prevent</i> the logs from being overwritten.		
EHRCR-T0-BR.400 There are sufficient system and/or process controls for	CSUCI EU Annex 11 ICH GCP	A	This may be handled via the site operating system and associated procedures or via the EHR system.	

backup and recovery procedures			The site is responsible for ensuring the backup and recovery method is working and documented.	
EHRCR-T0-DS.450 System limits the number of log-in attempts and record unauthorized access log-in attempts.	CSUCI EU Annex 11	A	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.	
EHRCR-T0-DS.460 System allows and enforces password or other access keys to be changed at established intervals.	CSUCI EU Annex 11	A – does not fully comply; site must set up rule to force pw change	Site must ensure that this feature is installed and turned on. The site is responsible for establishing reasonable intervals.	
EHRCR-T0-DS.470 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	A MU	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.	
EHRCR-T0-DS.480 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	A	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.	
EHRCR-T0-DS.490 The system has the ability to create, maintain and apply the roles, access permissions and capabilities of each user that accesses the system,	CSUCI Part 11 EU Annex 11	A+CR MU	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	

such that users have access only to those system features and functions to which they have been granted access.			accounts to users upon justification of their need for an account. A process should be in place to ensure that access is removed when an employee no longer has justification for using the system (such as getting assigned to a different area or leaving the organization.) If you are using a hosted system, be sure that the vendor will provide the user administration and that you understand the process for obtaining and removing accounts.	
EHRCR-T0-DS.500 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	A	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.	
EHRCR-T0-DS.510 System allows audit trail to utilize standard time-keeping method such that the local time can be derived.	CSUCI	A	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.	
<b>Process User Requirements</b>				
EHRCR-T0-BR.550 Process and/or system controls ensure data used for clinical research source records are retained for the legal period.	CSUCI Part 11 EU Annex 11 EU Directive 2005 28 ICH GCP	A – system provides feature, however must be set up with site controls for legal retention	Sites are responsible for knowing the legal retention period and for ensuring that methods employed to meet this requirement are working.	

EHRCR-T0-DS.600 There are sufficient system and/or process controls to prevent or mitigate effects of viruses, worms, or other harmful software code	CSUCI EU Annex 11	N/A to system certification, however individual sites must comply	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.	
EHRCR-T0-BR.650 There are sufficient process control for the system covering Disaster Recovery Procedures / Contingency Planning	CSUCI EU Annex 11 ICH GCP	N/A to system certification, however individual sites must comply	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.	
EHRCR-T0-BR.700 The site has documented procedures for controlling user process at the site (system security measures, how source data are obtained and managed, what electronic systems are used)	CSUCI Part 11 EU Annex 11 ICH GCP	N/A to system certification, however individual sites must comply		
EHRCR-T0-DS.750 The site has documented procedures for maintaining a copy of the source data at another location other than the clinical site	CSUCI EU Annex 11 EMA	N/A to system certification, however individual sites must comply		
EHRCR-T0-TR.800 There is 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	N/A to system certification, however individual sites must comply		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
EHRCR-T0-SV.850 There is a vendor process to demonstrate that development and	CSUCI Part 11 EU Annex 11	N/A to system certification, however individual sites must comply	An audit of the vendor must be performed to determine if this requirement is met. This requirement is not part of the	

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.			EHRCR functional profile as it is not part of the functions of a system.	
EHRCR-T0-SV.860 There is a research <i>site</i> 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	N/A to system certification, however individual sites must comply	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) necessary to comply with clinical research requirements. All validation/testing activities should be documented such that they can be audited by the sponsor or inspected by a regulatory agency. If the system is upgraded to a new version the changes might require validation, depending on the extent and the scope of the changes. The site must keep track of what version of the system was in place on what date.	
EHRCR-T0-IO.900 There is a system function	CSUCI ICH GCP	A		

and/or process to ensure the ability of the site to provide a cumulative directory of all personnel who use or access the data for the trial.				
EHRCR-T0-DS.950 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 administrator privileges.	

## APPENDIX 1: Glossary

ASP	Application Service Provider – vendor of a system might offer to host that system for your use.
CCHIT	Certification Commission for Health Information Technology (US) (CCHIT®), is a nonprofit organization with the public mission of accelerating the adoption of health IT. CCHIT is an ONC (Office of the National Coordinator for Health) Authorized Testing and Certification Body.
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)
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. ) Sponsors of the Q-Rec project for Quality Labeling and Certification of Electronic Health Record 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
IHE	Integrating Healthcare Enterprises
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
MU	Meaningful User Certification (US): The US Medicare and Medicaid EHR Incentive Programs provide a financial incentive for the "meaningful use" of certified EHR technology to achieve health and efficiency goals. By putting into action and meaningfully using an EHR system, providers will reap benefits beyond financial incentives—such as reduction in errors, availability of records and data, reminders and alerts, clinical decision support, and e-prescribing/refill automation.
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.
RFD	Retrieve Form for Data capture
SOP	Standard Operating Procedure
Sponsor	Clinical research sponsor (e.g. bio-pharmaceutical company)

## **APPENDIX 2: Discussion of Regulations and Guidances applicable to Clinical Research electronic source data**

### ***A. 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 and 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*.

Predicate rules 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 maintain, create, archive, retrieve or transmit electronic records which pertain to these predicate rules must comply with the applicable statutes and regulations noted above. 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 electronic record is being used 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). We have devoted a complete section to Part 11, as an understanding of Part 11 compliance may also help in complying with other related regulations.

## **B. 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'*.

These guidelines go into effect June 30, 2011; and in some EU member countries, Annex 11 may be applied on a statutory basis

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 not realize that Annex 11 applies to them. But that argument is becoming more difficult to make as EHR systems store increasing amounts of electronic source data used for clinical research. This is not a guidance (or, as applied in some countries, a statute) that should be feared by the healthcare industry.

As explained above for Part 11, Annex 11 is a similar very good guideline for maintaining and protecting the integrity of electronic records, and its requirements may already be met by the healthcare industry in using standard best 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.

## **C. 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. ICH covers multiple topics across pharmaceutical

research. The applied principles of ICH E6 (R1) are known as ‘Good Clinical Practice’ or GCP.

ICH E6 (R1) GCP when practically applied to systems (e.g. functional and procedural controls, audit trails, system use, and training) should largely be met by the application of the requirements as described in Part 11 and Annex 11. Therefore, compliance with ICH GCP principles should not cause undue concern by the healthcare industry and is most likely already being met by EHR systems that follow best practices in order to keep patients safe.

#### ***D. 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 (95/46/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 abiding by these laws, we will not go into great detail regarding them in this paper.

#### ***E. 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.” CSUCI was used as one of the basis documents for the EHRCR User Requirements.

#### ***F. EMA Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials***

The European Medicines Agency released this reflection paper in August 2010, after 3 years of deliberation over a draft and subsequent industry comments. This is the first regulatory document that specifically states that it relates also to electronic health records when they are used as electronic source for clinical research. While it is a “reflection paper”, it must be taken seriously by clinical researchers as it states “Any departure from this paper would need to be justified.”

It echoes the CSUCI guidance in that it expects data and records to be: *Accurate, Legible, Contemporaneous, Original, Attributable*, and then adds *Complete, Consistent, Ensuring, and Available when needed*. It also reiterates the requirements of ICH E6 (R1) GCP as applied to electronic records. It states: “There should be no loss of quality when an electronic system is used in place of a paper system.”

This paper specifies that sponsors who conduct clinical trials are responsible for ensuring that the systems that originate the source data for these trials have provisions to ensure these are met. They should obtain proof that these provisions are working via a system assessment that includes “consideration of the potential harm to trial subjects and patient rights and to the data integrity of the trial.” This would include secure audit trails, procedures to prevent practices such as password sharing, as well as procedures for managing archived data during and after the trial has completed. It also notes that monitors, auditors, and inspectors are expected to have direct access to the entire electronic health record of patients who are on clinical trials.

The reflection paper draws heavily from the Clinical Data Interchange Standards Consortium (CDISC) eSDI paper (Nov 2006) titled “Leveraging the CDISC Standards to facilitate the use of Electronic Source Data within Clinical Trials”.

The requirements in this reflection paper are broader than the ones in our user requirements and essentially support ICH E6 (R1) GCP requirements. Therefore, there are few specific references to this guidance in the table below. It is helpful to be aware of the overall guiding principles, however.

## APPENDIX 3: 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](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 governing clinical research

- European Union: <http://eur-lex.europa.eu/en/index.htm>
  - EU Directive 2001/20
  - EU Directive 2005/28
  - EU Annex 11
  - EU Directive 2001/83
  - EU Directive 2003/94
- EU Regulation 1902/2006
- U.S.A: [www.fda.gov](http://www.fda.gov)
  - 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](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
  - FDA 21 CFR Part 50, Protection of Human Subjects
  - FDA 21 CFR Part 54, Financial Disclosure by Clinical Investigator
  - FDA 21 CFR Part 56, Investigational Review Boards

- FDA 21 CFR Part 314, Applications for FDA Approval to Market a New Drug
  - FDA 21 CFR Part 812, Investigational Device Exemptions
  - Federal Food, Drug, and Cosmetic Act (the Act)
  - Public Health Service Act (the PHS Act),
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>
  - EMA Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials. (August 2010)  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2010/08/WC500095754.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf)
  - U.S. FDA, Guidance for Industry, Electronic Source Documentation in Clinical Investigations (Draft, Dec 2010).  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM239052.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](http://www.cdisc.org/single_source/about.html)
  - HITSP (Healthcare Information Technology Standards Panel)  
<http://www.hitsp.org> (note: this organization was dissolved on April 30, 2010, however the website is still a good reference)
  - Integrating Healthcare Enterprise (IHE): <http://www.ihe.net>
5. EHR Certifying Bodies

- CCHIT – Certification Commission for Health Information Technology:  
<http://www.cchit.org><sup>4</sup>
  - 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](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>