

Healthcare Link User's Guide

Clinical Research Data Capture

Introduction

Healthcare Link is a CDISC initiative with the overarching goals to make it easier for physicians/healthcare sites to participate in sponsored clinical research; to collect data only once (in an industry standard format for multiple downstream purposes; and, to improve data quality and patient safety (<http://www.cdisc.org/healthcare-link>).

The technical progress for Healthcare Link has largely emanated from a collaboration between CDISC and Integrating the Healthcare Enterprise (IHE). The Healthcare Link initiative aspires to create an integrated system for clinical research participation at healthcare sites, from protocol eligibility through reporting and submission. This User's Guide addresses one segment of that aspiration: clinical research data capture at healthcare sites.

The current state of research data capture is illustrated by figure 1. Despite much progress,



Figure 1

research data at healthcare sites continues to be collected through a mish-mash of paper, and various Electronic Data Capture (EDC) systems. Meanwhile the Electronic Health Record (EHR) takes its rightful place as the central application for healthcare automation. Much of the data collected for research is often already contained in the EHR, and is then duplicated on paper or EDC for research. Healthcare Link provides an integrated system that positions the EHR as the single user interface for healthcare staff supported by interoperable workflow automation with the EDC, which retains its important

role in data capture, clinical trial automation and data curation.

CDISC has worked closely with IHE's Quality, Research, and Public Health (QRPH) domain to create a set of integration profiles that creates this interoperability. The development of the healthcare link profiles was guided by these principles:

- Use global research standards (CDISC) for research purposes; healthcare standards (HL7) for healthcare purposes.
- Use research systems (EDC) for research automation; healthcare systems (EHR) for healthcare automation.
- Respect the separate regulations that apply to healthcare and research, following 21 CFR Part 11 for research; and HIPPA for healthcare.
- Keep the needs of the healthcare sites in mind, integrating the workflow of site-based research activities into the EHR.
- Invent integration approaches that make it easy for EHR systems to support research and which preserve and expand the role of EDC systems.

Unlike single application solutions such as EHRs and EDCs, Healthcare Link is by definition and by design a multi-system solution. Such integration of two or more component systems requires specifications that addresses each system's role, and defines the 'dance steps' which each system performs. Hence, this User's Guide takes different perspectives into account in order to align the complementary roles that each system plays.

Each component system within Healthcare Link assumes clearly defined roles which are specified in IHE integration profiles. These IHE profiles (RFD and CRD, see Scope below), describe the roles to be played, and define the transactions that each system executes. At least three independent systems participate in the integrated Healthcare Link solution: an EHR, an EDC, and an Archive. In a particular implementation, supporting one clinical study, there can be many EHRs, but usually only one EDC, and one Archive. Conversely, a clinical site that conducts many studies for different sponsors has only one EHR, but may interact with many different EDCs.

Scope

The intent of this guide is not to replace the technical details for building a Healthcare Link solution by implementing the profiles, but to augment them with additional information about how the participating systems, the EHR and EDC and Archive, should approach an implementation. IHE integration profiles explain how the interoperability between EHRs and EDCs works. Links to the IHE specifications can be found here:

http://www.cdisc.org/system/files/all/standard_category/application/pdf/cdisc_healthcare_link_profiles.pdf.

These IHE profiles contain both subject matter and technical information. Volume 1 of an IHE profile is intended for a non-technical audience, and includes a narrative use case that illustrates the before-state and the after-state of implementation. Volumes 2 & 3 are technical documents which allow cooperating technicians to create an interoperable solution across systems. Prospective implementers should read the specifications in their entirety. This User's Guide will not re-state the profile actor and transaction specification, but will discuss in more detail how the participating systems do the work, and the activities needed to set up a project using Healthcare Link.

The "dance moves" for transactions between the EHR and EDC are defined in two IHE profiles: Retrieve Form for Data-capture (RFD), which brings up the appropriate form, and Clinical Research Document (CRD), which populates the form with EHR data (when such data exist). There are more profiles within the healthcare link body of work, but RFD and CRD are the core, as well as the most mature and implementable. Together RFD and CRD allow an EHR user to fetch a partially pre-populated electronic case report form (eCRF), and to complete the form within the EHR's user interface. But since eCRF completion takes place in the middle of a research protocol execution, RFD and CRD do require protocol specific configuration. This configuration is automated by newer profiles such as Retrieve Process for Execution (RPE), but until the newer profiles are ready for implementation, this user's guide will provide the configuration details (see Roles of each system below).

RFD can be implemented by itself whereas CRD, which defines the content for form pre-population, cannot be implemented without RFD. Nextrial's Robert Barr, an early RFD implementer, explains the value of implementing RFD even without pre-population of the form:

"In demonstrating the RFD profile to actual customers and partner companies, the use of RFD without pre-population has come up many times. The flexibility of the RFD profile allows us the option to create a "Lite" version of our system that a customer can use for a simple, straightforward entry point to specific forms. They may not have pre-population, but still want to surface a form at the right time and place from within their interface. They are able to utilize the existing profile and calls, allowing them direct access to our forms without going through all the login and navigation to get to that one specific form."

So, RFD by itself simplifies the workflow for site data entry; but, even greater benefits come with pre-population, which is the province of CRD, and the focus of this User's Guide.

Functional Description of RFD and CRD

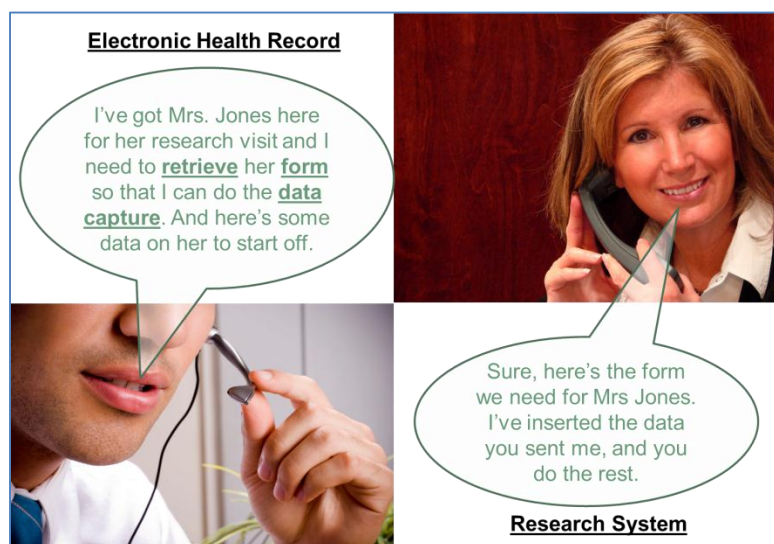


Figure 2

RFD and CRD, once implemented, set up a conversation between the EHR and the EDC system. The EHR and EDC, pictured as characters carrying on a phone conversation in figure 2, illustrate the first RFD transaction. The EHR system initiates the conversation by requesting the appropriate form from the EDC. This request is accompanied by a set of data elements for use in auto-population. The EDC system responds by mapping the

EHR data to its form and returning the partially populated form to the EHR. Taken together, this request/response exchange constitutes the eponymous ‘retrieve’ in RFD.

The conversation continues in figure 3, with the EHR now having displayed the pre-populated form in the EHR’s user interface.

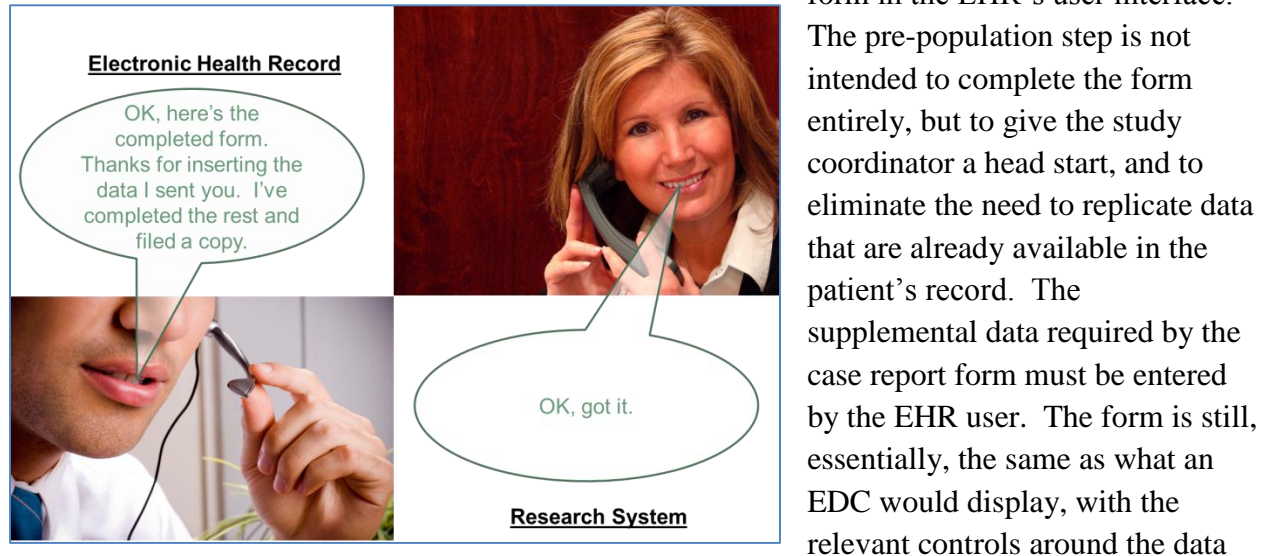


Figure 3

to be entered. In other words the form will catch egregious errors such as out of range values and mismatches between demographics and conditions, i.e. a pregnant male.

The EHR does not necessarily store the data collected in service of the research study. The standard is silent on this point, but the common practice is for the EHR to allow the EDC to contain and control all data elements specific to the study, while the EHR restricts itself to data relevant to patient care. The case report form surfaces in the EHR’s user interface, but retains its connection to the EDC. As such, the form is an island of research within the EHR’s workflow, and the EHR can maintain an arm’s length relationship to it.

Upon completion of the form, the data are delivered to the EDC and also to an archive. There only remains the final step in which the EDC system acknowledges receipt of the completed form.

The conversation results in completion of a case report form which combines the rigor of EDC designed forms for data capture with the convenience of integrating the functionality in one user interface, the EHR.

Figure 4 gives a more technical visual of the conversation. This schematic shows the transactions between the EHR and EDC systems, and shows the independent actions required by the EHR and EDC to set up and fulfill the requirements of the transactions. Figure 4 does not

include the archiving step. For a complete rendering of the activities of the two systems, see the RFD and CRD profiles.

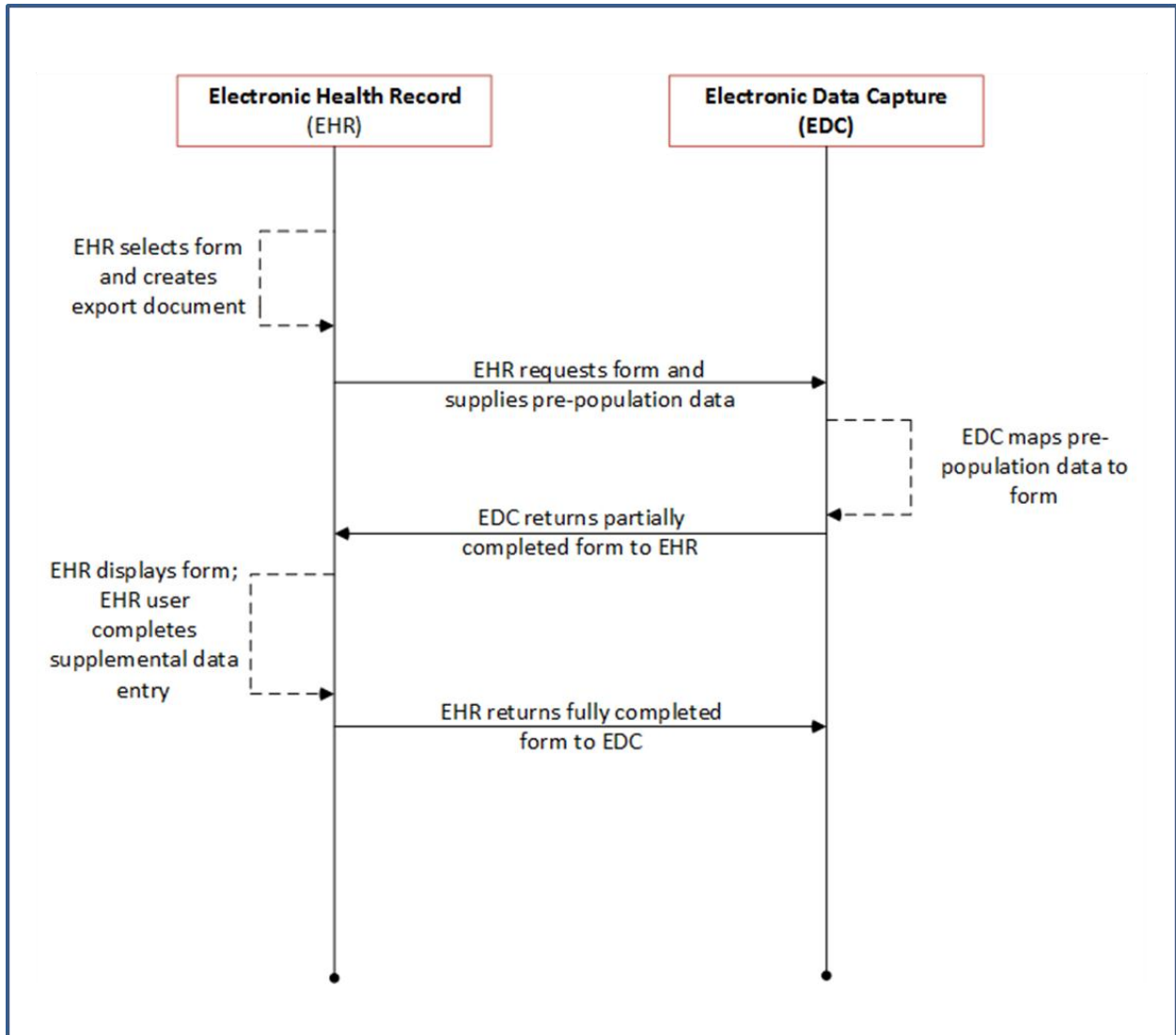


Figure 4

Using Healthcare Link

At the clinical study level, the implementation of Healthcare Link is fundamentally no different than the implementation of data capture systems and processes commonly in place, but with the benefit of simplified process for data capture and processing for the sites. The key considerations are:

- Selecting tool(s) for data capture
- Identifying roles and processes
- Ensuring compliance to regulations as embodied in relevant SOPs

Selecting Healthcare Link Capable Systems

As presented earlier, there are three key systems needed for Healthcare Link data capture: EDC, EHR, and Archive. Many organizations conducting clinical studies will already have an EDC system in place, or will select one of the many commercially available systems. Some EDC systems will already have implemented the IHE profiles. The clinical sites involved in a study will likely have different EHRs, so a list of all EHRs to be encountered for a study must be compiled for consideration.

The systems selected must meet the requirements that RFD and CRD specifies for their role, including the transactions that are sent and received among the participants. For a new implementation involving a new combination of EDC and EHR systems, testing transactions among systems selected should be part of the development process. IHE hosts annual Connectathons in North American and Europe, providing opportunities to test systems implementation of the profiles in a structured environment. More information regarding Connectathons and the schedule for Connectathons can be found at <http://www.ihe.net/connectathon/>. For studies that use EDC and EHR system that already have the profiles in production and can make the needed transactions, the focus can be on the study specific configuration. In addition to this, each vendor must be prepared to adapt their tested system to the exigencies of real world installations.

Implementation – Systems and Roles

Implementers of the healthcare link approach for a particular research profile fall into three roles: one EDC, one or more EHRs, one or more archives.

Role of the EDC

As described in the FDA eSource guidance (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf>), “The eCRF is a vehicle used to assemble all the data from different electronic- and paper-based systems and makes it possible to capture and organize these diverse data in a manner that satisfies the study protocol . . .” The role of the EDC system in Healthcare Link provides the eCRF, and the EHR is the primary source of data, replacing paper-based

“source” documents. The eSource guidance then calls for the source to be available for inspection, with information on “the ability of the software to transfer accurate and complete data from the electronic health record into the eCRF.” The implementation of Healthcare Link with the two IHE profiles – RFD and CRD – provides an established technical framework and details on how the data are transferred properly from EHR to the eCRF.

The selected EDC system plays a major role in study specific configuration to achieve the implementation of Healthcare Link. Considerations for the role of the EDC include:

1. Ensure EDC system is compatible with the latest RFD and CRD standards, in addition to CDISC Operational Data Model (ODM) and Clinical Data Acquisition Standards Harmonization (CDASH) [ODM Certification is recommended.]
2. Review compatibility with Retrieve Process for Execution (RPE) standards as needed.
3. Work with potential sites
 - a. Identify compatible EHRs at study sites
 - b. Ensure EHR versions are RFD compatible
4. Work with site/EHR vendor on study configurations
 - a. Add study ID’s, Site ID, Investigator ID, as per CRD needs, and endpoints to EHR configurations
 - b. Add study archive endpoints to EHR configurations
 - c. Verify feature options implemented in EHR such as enrollment
 - d. Verify security configurations between EHR and EDC systems.
5. Define CRF design and field mapping for CRF’s from CRD
 - a. Verify field mapping by site / EHR, make adjustments as needed.
6. Review relevant security configurations by site with EDC system
 - a. User security
 - i. SAML
 - b. Site Security
 - i. Certificates
 - ii. Pre-Shared ID’s
 - c. Transaction Audit Logging
 - i. Based upon Security considerations, setup and configuration of an Audit Repository may be necessary.
7. Site go live
 - a. User acceptance testing of CRF mappings
 - b. Connectivity testing
 - c. Security verification
 - d. User training

Role of the EHR

The main feature of Healthcare Link is that it moves the clinical research activities to the EHR interface. For most sites, the EHR is the central repository of all original patient data. Some data, such as those from study protocol specified assessments such as central labs, may by-pass both the EHR and entry into the eCRF, and be compiled separately for study purposes. At sites

with more comprehensive EHR capabilities, all such external data may also route to the EHR. As more data are consolidated in the EHR, CRD will be able to populate more of the eCRF in EDC, leaving only those assessments that are truly unique to the study to be entered as a transaction within the EHR interface through RFD.

Because the EHR is inherently part of the site's operations, there will not be an opportunity to choose which EHR system to use on a study. Most of the sites conducting clinical research will also not have the ability to modify their own EHR installation. As such, the designers of RFD and CRD have worked to ease the burden of participation on the EHRs, recognizing that research support is not a core role of this healthcare application. Therefore, where ever possible, the burden of work was reserved to the EDC system. What remains are a few key steps for the EHR to participate in a Healthcare Link implementation.

1. The EHR must record several facts about the patient's involvement in a research study, as defined in CRD and in conjunction with study specific requirements in the EDC; this Enrollment content is likely to be collected and entered manually today.
 - Subject identifier
 - Study identifier
 - Form identifier
2. The EHR must configure the EDC endpoint for the Retrieve Form request.
3. The EHR may need to configure an endpoint for an archiver:
 - To be sent during the Retrieve Form request to document the transaction.
 - To provide a copy of the patient data as source documents.
4. The EHR should provide a trigger to summon the eCRF, and must know the form identifier.
 - It is expected that this trigger shall be patient specific, and thus should be able to map the EHRs patient/patient identifier to the CRD parameters:
 - Form Identifier
 - Subject identifier
 - Study identifier
 - Possibly Investigator identifier and other CRD parameters
5. The EHR must create, on demand, an export document that meets the specifications of the CRD.
 - This content shall be included with the Retrieve Form request as specified in CRD and RFD.
6. If required by the Security analysis, the EHR shall submit source documents prior to the Retrieve Form request.

The Archiver

The archiver plays the role of collecting and storing eSource documents as the 'black box recorder' of the study. The archiver captures two documents that, together, enable electronic source documentation. The first document, the CCD that the EHR exports for pre-population, documents the source of the pre-populated data elements. Since this document contains identifiable patient health information, it is essential that the archiver remains within the purview of the site. The second document, the completed form instance, shows how the pre-populated

data elements appear in the completed form. This second document is an exact replica of the completed eCRF as submitted to the EDC system. By comparing the EHR's export document to the submitted eCRF the provenance of the data can be inferred.

The archiver is designed specifically to meet the source documentation requirements of 21 CFR 11, and the FDA eSource Guidance, found here:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf>).

The key capabilities of an Archiver are:

1. Determine the reporting source for data it receives;
2. Able to receive all data elements;
3. Assurance to not alter the content of the data it receives in any way;
4. Associate all of the data elements that come from a single instance of a form with one another;
5. Create a reliable persistent copy of all of the data elements and their association with a single occurrence of a form submission;
6. Never allow any received data to be altered by anyone in any way; and
7. Provide a mechanism by which an external system can view or download a copy of the data based on some filtering criteria.

The standard specifies the capabilities that are essential for source documentation but is intentionally silent on how these capabilities are packaged. This open approach allows archive developers the freedom to differentiate their product. A fully featured archive would enable source document/data verification from 'afar', thereby reducing or eliminating the need for on-site verification.

Compliance

The operating procedures and practices used in the conduct of a clinical study using EDC are well established, and it is assumed that the EDC system selected for any implementation of Healthcare Link will be compliant with the usual requirements such as:

- Computerized Systems Used in Clinical Investigations
- General Principles of Software Validation
- 21 CFR Part 11, Electronic Records; Electronic Signatures

The added interactions with the EHR do highlight some additional considerations regarding privacy, and that the source study data are in electronic form that is not controlled under FDA requirements as EDC systems are. EHR by definition, is a system that contains protected health information and by necessity is linked to many other systems such as pharmacy and billing that cannot be covered under research guidances. Healthcare Link narrowly defines the scope of the

EHR and provides the proper documentation and processes that address the concerns that arise from these additional considerations.

Privacy

A key tenant of clinical research data is that subject data in the research database (EDC) should be masked, while data in EHR will include not only personal health information, but links to insurance and financial records, with penalties for the unauthorized release of such data. The privacy requirements have caused concerns about accessing EHR data for research purposes. However, the data being used in the study via Healthcare Link should not violate any privacy requirement. The data elements are defined and controlled by EDC via RFD, and the data being populated are extracted via CRD. As the practice within research does not include personal identifiable data other than what is customary and needed for research, there should not be any increased risk to individual privacy.

Privacy for research subjects is provided through pseudonymization, whereby the study identifier is linked to the patient identifier in the EHR, but not in the research system (EDC). All Healthcare Link transactions employ only the subject identifier, providing a firewall against improper identification of the patient. Only the EHR can put the subject identifier and the patient identifier together. In cases of subject safety, the EHR can ‘break the glass’ and identify the subject’s patient identity according to the principle that ‘safety trumps privacy’.

Privacy concerns due to unauthorized intrusion to the system are left to the individual systems. The EHR itself outside of Healthcare Link should have protective measures already in place to meet its own data privacy needs. Healthcare Link does not define what is needed for a well-protected system as systems and technology is constantly evolving. As a preparatory step for any cross-enterprise undertaking, a Security Considerations Risk Analysis should be performed. The details of the assets, threats, and mitigations will determine the use of certificates and TLS, SAML, and Audit Logging for the communications between the systems.

Supporters

The Role of CDISC

As the originator of the Healthcare Link initiative, CDISC is responsible for bringing the concept of EHR-enabled research to reality. CDISC continues to work with IHE’s Quality, Research and Public Health (QRPH) domain to introduce new profiles and to improve existing profiles through IHE’s process of testing and change proposals. In this role, CDISC, with its IHE partners, controls the pace and direction of Healthcare Link profile creation.

At a more fundamental level, CDISC provides core standards that provide the foundation for the IHE research related implementations. All IHE profiles build upon existing core standards such

as CDISC's ODM and CDASH and HL7's CDA. So as Healthcare Link evolves, the CDISC standards come into their own as the 'target' of the secondary use of EHR data.

In addition to its direct developmental role with IHE, CDISC assumes broad responsibility for promotion and realization of Healthcare Link's value. These processes include:

- Industry advocacy: CDISC, through its communications and education efforts, promotes the uptake of Healthcare Link.
- 'Matchmaking': since Healthcare Link requires collaboration among a set of EHRs, EDCs, sites, and research sponsors, CDISC seeks to align incentives to promote implementations.
- Regulatory advocacy: CDISC has presented healthcare link to audiences at FDA and to other regulatory agencies. Comments from FDA have been incorporated into IHE's research related profiles through the change proposal process.

The Role of IHE

The role of IHE in Healthcare Link is aptly described by this paragraph from the IHE Radiology User's Handbook.

IHE is an initiative by healthcare providers and vendors to improve the way information systems communicate to support patient care. IHE defines Integration Profiles that use established data standards to integrate systems for effective interoperability and efficient workflow. IHE makes it possible to achieve the level of integration required in the era of the electronic health record. Each IHE Integration Profile describes a requirement for systems integration and a solution to address it. It defines functional components, called IHE Actors, by specifying in careful detail the transactions, based on standards such as CDISC and Health Level 7 (HL7), each Actor must perform.

In addition to its role in developing integration profiles, IHE provides a means for software vendors to test profiles at annual Connectathons in North America and Europe. The RFD profile has been widely tested, resulting in final text status. CRD has had limited testing, and remains in trial implementation status.

Perhaps the greatest value of IHE to the research community is the contact with willing collaborators from the EHR and public health sectors. RFD and the other healthcare link profiles were developed by an engaged and active community of contributors, and RFD has attracted interest beyond research, specifically in the public health and quality reporting realms. IHE's open process and evolving body of work provides a fertile field for further development. Users of this work, especially early adopters, should not view the profiles as finished products, but as an open ended effort that welcomes input.

Conclusion

This User's Guide is intended as a general overview of Healthcare Link capabilities pertaining to data capture for clinical research. This guide in no way replaces or competes with the two IHE profiles RFD and CRD which enable clinical research data capture. Any serious interest in the topic must quickly lead to a reading of the actual profiles, the CDISC standards and a consideration of the partnerships which implementing these profiles requires. CDISC stands ready to help potential implementers to get started through education, "match making", and standards advocacy. CDISC also provides a Healthcare Link course through authorized CDISC Education.