The Time is Now

The convergence of electronic health records and clinical research is changing the way the pharmaceutical industry operates. Jacob Helton, Landen Bain and Rebecca Kush of the Clinical Data Interchange Standards Consortium (CDISC) and Linda King of Eli Lilly and Company investigate an evolving landscape.

The development of a patient-oriented healthcare environment that can enhance patient safety and reduce healthcare costs is greatly needed (1). In order to help meet this need, a transition from paper-based patient health records and source documents to their electronic equivalent has been occurring, as evidenced by the utilisation and global adoption of the electronic health record (EHR). Though a dedicated electronic data capture (EDC) system that is able to capture essential clinical research data can be considered a very good asset, the associated process can be improved for an investigative site through integration of the EDC capabilities with an EHR. A pragmatic solution involves a more comprehensive system, such as an extended EHR, that can efficiently update data capture and support a framework that allows for the exchange of healthcare and clinical research data, while meeting the existing regulations, allowing for more efficient clinical care and clinical research processes (1).

Currently, moving the case report form (CRF) to the EHR is being resolved and a viable solution has been demonstrated. Therefore, clinical research conducted via extended electronic EHRs can provide several advantages to healthcare providers, clinical researchers, and their patients. These advantages will enhance best practices and include:

- A reduced burden placed on healthcare professionals conducting clinical research
- An increase in the quality of data captured during clinical research processes
- Improved patient care
- Improved product and patient safety

**THE VALUE CASE FOR CONDUCTING CLINICAL RESEARCH USING EHRs**

Clinical research enabled EHRs to reduce the time requirements placed on healthcare providers and data coordinators due to the reduction in the number of times that the data must be manipulated. Data from EHRs can be re-used for multiple purposes including clinical studies, safety reporting and trial registries (2). EHR efficiency gives the clinician greater opportunities for extracting knowledge for both patient care and clinical research. An individual clinician can generate his or her own patient care institutional memory that will extrapolate to better care and clinical research. In addition, more healthcare providers may be willing to participate in clinical research, due to the enhanced ease with which EHR data can be collected and, of course, the associated benefits to their patients. Similarly, improved data quality should occur due to a reduction in transcription errors that can occur during the re-entry of data into an EDC system (2). In particular, direct data extraction may be the future basis of predictive and evidence based medicine.

Patients can also benefit through the use of healthcare providers that utilise EHRs in a global or federated clinical database system. Enhancements to patient safety can be attributed to three potential occurrences. First, since there is no need to transcribe protocol-defined information into a sponsor-provided EDC system, multiple entities will have real-time access to the patient’s study information (2). Second, healthcare providers will gain access to a larger pool of the correct patient population for clinical research, increasing the probability the appropriate patient will be screened for a clinical trial. Finally, an increase in patient safety will result from an improved spontaneous serious adverse event (SAE) reporting system.

**CONSIDERATIONS FOR CONDUCTING CLINICAL RESEARCH USING EHRs**

There are several considerations which must be taken into account if and when EHRs are going to be utilised for conducting clinical research. First, for regulated research, the electronic environment must adhere to the existing regulations and guidances (such as 21 CFR Part 11, 312.62(b), ICH guidelines/GCPs and CSUCI) (1). Another concern is related to the desire of clinicians to maintain a normal workflow process in her or his clinical care while conducting research. Furthermore, EHR vendors prefer solutions that do not include the need to make major changes to their existing applications. The ability of EHRs to exchange data readily with clinical research tools is needed and is now ready for first implementation. The final consideration, and the key to utilising EHRs as the primary link between the healthcare and clinical research industries, is that the components which constitute the electronic environment must be flexible. That is, the vendor, site and study sponsor must be able to utilise any EHR and any EDC/CDMS that supports an open global data transfer standard (such as CDISC) and the Integrating the Healthcare Enterprise (IHE) initiative’s Retrieve Form for Data Capture (1).

**CONTEMPORARY SOLUTIONS**

In order to determine if a new technology meets the standards and regulations of its users, a fundamental set of 12 guidelines, based upon global regulations, was developed (1). The 12 guidelines were created to help define the fundamental requirements for using electronic source data. The regulations...
set forth by the FDA best practice guidance, 21 CFR Part 11 and the ICH Good Clinical Practices are expected to be met if these 12 guidelines are followed when setting up the method and process for using an EHR for clinical research. It is these guidelines that formed the basis for the IHE RFD integration profile.

The CDISC-led Clinical Data Acquisition Standards Harmonization (CDASH) project, one of the FDA Critical Path Initiative Opportunities, addresses relevant data collection element standards for clinical research. In addition to establishing data collection standards based upon regulations and the recommended FDA eSubmission data format, study data tabulation model (SDTM), the CDASH goals included enhancing the data interoperability between clinical and medical research data by restructuring the process through which data are collected and improving the interface with healthcare and EHR (www.CDISC.org).

Comprising clinical research and healthcare industry professionals, the IHE initiative was developed to improve the capability of healthcare computer systems to share information (www.IHE.net). The IHE RFD has emerged as a practical solution that can be applied to prospective research and that will help ameliorate many of the current EHR inefficiencies. CDISC’s CDASH project defines the data elements common to all CRFs. As such, it gives the EHR community a clear ‘target’ – a set of data elements that should be provided to any clinical research data requestor. IHE’s quality, research and public health domain has developed a content profile called clinical research data capture (CRD), which specifies CDASH as the output.

The intention of RFD and its related IHE profiles is to extend the functionality of EHRs to include a mechanism for clinical research data capture. As previously mentioned, data capture for research, separate from data capture for clinical care, via existing disparate data capture systems, can be burdensome for healthcare professionals. Improvements to the process, and the quality of data captured, can occur by allowing external entities (that is, research sponsors) to participate in data collection while the EHR is active, allowing for real-time response to possible safety concerns. In addition, RFD facilitates the automatic re-use of previously entered data into the EHR through the use of content profiles such as CRD. Additional advances associated with RFD include:

- Reducing the number of data capture systems required at a site
- Enabling the FDA requirements to facilitate active surveillance of evolving or emerging signals of drug safety
- The enhancement of post-approval pharmacovigilance reporting
- Supporting risk minimalisation action plans and risk evaluation minimalisation systems
- Minimising the gap between healthcare and clinical research information
- Providing a means for immediate implementation of an extended EHR for clinical research

**CURRENT RFD IMPLEMENTATIONS**

RFD has matured to a point where implementations can take place spontaneously, without the need for external assistance or without risking a beta test. Three such adoptions make the case:

- APHP, the largest hospital system in Paris, France, developed a unique approach through their own reading of the RFD specification
- Hamamatsu University has begun the use of RFD to export data from their EHR, with a goal toward wider adoption throughout Japan
- Outcome Sciences, an eClinical company, and Greenway Medical, an EHR, have struck a deal built around RFD implementations in which Greenway Medical’s Prime Suite EHR will gather data via RFD to populate Outcome’s registries and observational trial CRFs

These spontaneous and diverse adoptions are the result of three trail-blazing projects:

**Adverse Drug Event Spontaneous Triggered Electronic Reporting (ASTER)**

The Pfizer-sponsored project seeks to improve pharmacovigilance at the point of care by using RFD to present drug safety forms in the longitudinal medical record (LMR) system at Partners Healthcare in Boston. The overall design of this effort is to create a new business model for post-market safety reporting by integrating RFD with services and infrastructure from Clinical Research Information eXchange (CRIX) into a novel design to collect higher quality data directly from EHRs and make it easier for physicians to report adverse drug events.

**Eli Lilly-Cerner-Quintiles-IPL**

Eli Lilly and Company, along with its partners, Cerner, Quintiles and IPL, are focused on confirming the RFD process and mapping the CDASH data elements to EHR data elements with the intent of minimising data transcription errors, and gaining a better understanding of eSource data. Eli Lilly’s intent has been to use the RFD process in real-life settings implemented at real sites. Through this project, they are developing and confirming the site workflow and the process of submitting the data directly from the EHR into a clinical data management system, as well as to a readable data archive to ensure compliance with FDA regulations. The project has demonstrated RFD using a real CRF from protocol derived from Lilly methods, but has yet to migrate from the demonstration setting to a real site.

**NIH**

NIH have sponsored a project to demonstrate RFD capture of data elements specified by the Basal Adverse Event Report for reporting adverse events associated with NIH studies to IRBs and other parties.

**THE FUTURE**

EHR integration is poised for a new wave of spontaneous adoption because of four factors:
The legitimacy and clarity of the EHRCR document (referenced previously)  
RFD's technical maturity  
The collaboration of eSource/RFD and CDASH  
The impetus of the FDA Sentinel Initiative

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The map of the future was clearly drawn by an EHR-CR paper and there is now an associated HL7 EHR-CR functional profile that is going through the HL7 standards-development process (3). EHR-CR is a global collaboration between the eClinical Forum and the EDC/eSource Taskforce within PhRMA. This group published a paper that defines their vision of how EHRs and eClinical systems will interact in three future ‘tiers’ of emerging and future connectivity and complexity; the paper and the HL7 EHCR Functional Profile standard define the clinical research requirements or the ‘what’ that RFD addresses with its technology solution, or the ‘how’.

RFD has now matured into a reliable, implementable solution, with spontaneous independent adoption in North America, Europe and Japan. IHE continues to expand RFD, and to complement the core integration profile with content profiles such as clinical research data capture and drug safety. RFD approaches its third testing and demonstration cycle and carries with it a body of best practice information from its early adopters. Thus, synergy between EHR-CR and RFD can finally overcome resistance shown by the biopharmaceutical industry to pursuing the use of EHRs in clinical research.

For clinical research, RFD combined with CDASH provides a minimal set of clinical research data to collect from an eSource application (EHR). The combination of RFD and CDASH paves the way for a sponsor to readily adhere to the SDTM standard requested by FDA for eSubmission and provides an available means of streamlining regulated research during the provision of healthcare. Finally, the FDA Sentinel Initiative opens a new impetus for EHR use. The Safety First/Safe Use initiative from CDER, which includes risk evaluation and mitigation strategies (REMS), will open doors for the more extensive use of RFD.

These post-market strategies emphasise real-world healthcare settings, and de-emphasise the more formal approach of traditional clinical trials. Instead, the focus is on collecting more data from more sites, and loosen the strictures of data capture in formal clinical trials. All of these strategies and implementations lower the barriers to the re-use of EHR data, with its looser structure but wider availability. These four factors combine to create a ripe opportunity for progress – the time is now.

References
1. CDISC eSDI (eSource Data Interchange): Leveraging the CDISC Standards to Facilitate the use of Electronic Source Data within Clinical Trials, 20th Nov 2006, www.cdisc.org/eSDI/eSDI.pdf