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eSource for Standardized Health Information Exchange in Clinical Research: A Systematic Review

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Abstract. The availability of research and outcomes data is the primary limitation to evidence-based practice. Today, only a fraction of clinical decisions are based upon evidence derived from randomized control trials (RCTs), the gold-standard of knowledge discovery. At the same time, clinical trial complexity has steadily increased as has the effort required at clinical investigational sites. Direct use of electronic health record (EHR) data for clinical trials has the potential to address some of these needs, improving data quality and reducing cost.

Keywords. eSource, electronic health records, secondary data use, clinical research

1. Introduction

Direct use of electronic health record (EHR) data in research has long-been a goal for biomedical researchers because of anticipated increases in data quality and reductions in site burden. Sporadic attempts toward this have been reported over the last decade [1,2]. However, to move beyond single-EHR, single-EDC (electronic data capture), and single-institution implementations, data standards and process re-design are needed as are rigorous evaluation of data quality, site effort, cost and feasibility.

Since 2010, over 20,000 clinical studies have been registered annually in clinicaltrials.gov with a 13% increase in the number of studies reported from 2015 to 2017 [3]. This is occurring at a time when clinical trial complexity continues to rise [4-9] and has resulted in escalating costs, forcing clinical development off-shore [10] and increasing site burden causing first-time clinical investigators to turn away from this work [11]. Reports have consistently articulated challenges and information-related workflow analysis and process redesign at clinical investigational sites are sorely needed [2,5,15,16]. Implementations of web-based EDC systems has not resolved the redundant and manual activities in site-based clinical research that significantly impede clinical trial research and has not reduced the overall costs. The need for advances in information management and use within clinical trials has been consistently articulated [5,6,9,12-16], and has spurred national initiatives such as TranCelerate and the Clinical Trails

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Transformation Initiative (CITTI). Formative work by Kim *et al.* distilled 42 distinct ways (14 use case categories) in which direct use of EHR data might improve clinical trials [17]. However, the clinical trial data collection use case is the most difficult and least demonstrated. Therefore, the objective of this systematic review is to identify and analyze the existing literature and current research efforts that aim to utilize direct, electronic EHR data extraction (eSource) and identify any gaps or limitations present for promoting standardized health information exchange in clinical research.

2. Methods

A survey of the literature was conducted to identify studies using direct EHR data extraction in clinical research. Several searches were performed in PubMed and Embase using the following key words: *eSource, EHR, direct EHR, EHR extraction, integration,* and *clinical research*. MeSH terms were also leveraged in order to address the various levels of search term specificity. Results were deduplicated prior to the application of inclusion and exclusion criteria (Table 1). Next, titles and abstracts were screened by two independent reviewers to further narrow the search results. The remaining articles were reviewed to identify articles relevant to eSource initiatives in clinical research settings, in which direct use of EHR data might improve clinical research.

Table 1. Inclusion/Exclusion Criteria

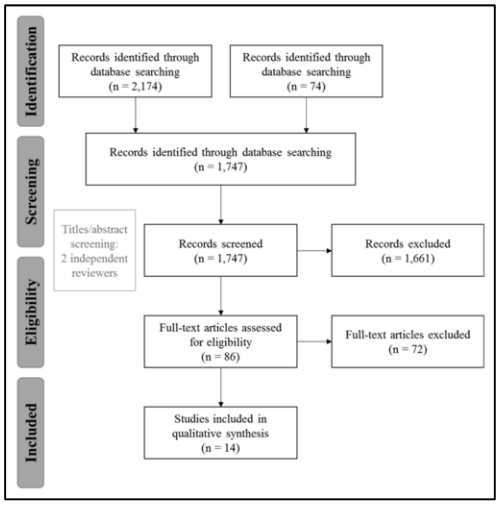
Inclusion Criteria	Exclusion Criteria
1. Solutions that utilize eSource to directly exchange data electronically from the EHR-to-EDC 2. Relevant to a prospective clinical study use case	1. Direct electronic EHR data extraction was not the main focus of the manuscript 2. Solutions not applicable to a prospective clinical study use case

3. Results

An initial search resulted in 2,174 articles. Seventy-four additional records were identified from other sources (i.e., reviewing reference lists and grey literature). After deduplication, a total of 1,747 articles were left for screening. Screening of titles and abstracts left us with 86 articles. A final screening of the remaining articles in full gave us a final total of 14 relevant articles (Figure 1). Most of the articles were excluded because (1) the research was not conducted in in the context of a prospective clinical study, (2) the manuscript was theoretical in nature rather than experimental, providing no true eSource solution for implementation or evaluation, or (3) the mechanism utilized for EHR-to-EDC exchange was not electronic and required significant manual processes.

Four critical dimensions were identified to categorize each study in relation to one another. These dimensions include (1) whether the study was conducted at a single site or was part of a multi-site study, (2) whether the study utilized a single EHR or multiple EHRs, (3) whether or not the study was conducted as part of an ongoing, prospective clinical study, and (4) whether or not relevant standards were used (see Appendix 1 for a complete summary).

Figure 1. PRISMA diagram



Eight of the fourteen manuscripts (57%) described single-site, single-EHR implementations. Of the six manuscripts describing multi-site studies, four were part of the same pilot study (EHR4CR European Pilot), a collaborative initiative across several European countries. Therefore, while the four manuscripts were each distinct in their interpretations of the study and their evaluative methods, and were included in this review, we would consider this to be a single eSource approach. Therefore, across the 14 manuscripts identified as part of this review, there were a total of 11 distinct eSource interventions evaluated. The majority of the interventions described (7 of 11) were not part of an ongoing, prospective study; and only 1 of the remaining 4 was a multi-site, multi-EHR implementation.

4. Discussion

Routine clinical documentation has long been used for research. Though the quality of medical records data and their use in research has long been questioned [18-23], the practice of medical record abstraction, by which a person reads all or part of the paper or electronic medical record, chooses desired data, and records the data onto a study-specific data collection form has been the mainstay of data collection in clinical trials [24]. However, medical record abstraction is time intensive, reliant on a human abstractor to sort through the uncertainty and inconsistency in medical records and is associated with high and highly variable discrepancy rates (median 647, average 960 discrepancies per ten thousand fields with a standard deviation of 1,018 from a large pooled analysis) [25]. To decrease and control the high error rate and variability of medical record abstraction, clinical trials have relied clinical trial monitors to verify collected data with the original medical records. However, the substantial cost and error rate from medical record abstraction remains. As part of a concurrent effort to evaluate and synthesize previously reported outcomes, we identified significant weaknesses and offer recommendations for improvement [26].

The use of eSource constrains medical records abstraction subjectivity and the opportunity for error in two very important ways. (1) eSource automates data abstraction and pre-populates the study-specific eCRF(s). This completely eliminates transcription errors and errors in pulling data from the wrong place in the record. This also reduces the time involved in medical record abstraction. (2) Where multiple values are available, they are displayed with the necessary context for the abstractor to select the correct value. As a result, eSource decreases cognitive load associated with medical record abstraction by representing them externally rather than requiring the abstractor to hold the information in working memory [27]. The efficacy of these mechanisms in reducing data error and abstraction time has been demonstrated [28-31]. We are now at the point where information systems leveraging data standards can increase clinical research efficiency and quality [32]. However, these methods need to be tested for effectiveness and acceptance in the context of real multicenter clinical trials. Several early studies using a single source of data for research and patient care appeared over a decade ago [2,33-34]. Since that time, implementations and evaluations have been scarce and almost always confined to single-EHR, single-EDC, single-institution implementations [35].

4.1 Single-Site, Single-EHR Implementations

In the STARBRITE project, Kush *et al*. demonstrated the feasibility of single clinical data capture with subsequent use in patient care and a clinical trial [2]. In the same year, Murphy *et al*. demonstrated custom-built EHR screens that included research data, which were later extracted from the EHR database [33], and Gersing and Krishnan designed a behavioral health EMR that integrated research and care [36]. During the same time, institutions began using warehoused clinical data to pre-populate prospective registries, including building registry data elements into the EHR [37]. Thus, there was early evidence that clinical data can be captured once and subsequently used for patient care and clinical research.

In 2009, Kiechle et al. reported an EHR-to-EDC pilot conducted in collaboration between Siemens and the Frauenklinik of the Technical University of Munich, called "the Munich Pilot" [29]. This study's technical solution consisted of a portal, an integration engine, and an adapted EDC system. This work leveraged HL7 messages in existing healthcare information systems [29]. Following receipt of an HL7 message from an EHR, the integration engine then translated the data into the Clinical Data Interchange Standards Consortium (CDISC) Operational Data Model (ODM, www.CDISC.org) exchange standard and stored the data in a validation buffer from which the data were displayed for human review, confirmation that the data belonged to the indicated patient, and initiation of transfer of the data to the EDC system [29]. The Munich Pilot demonstrated a statistically significant reduction in data collection time. However, there were too few data queries to assess this pilot study's impact on data quality [29].

In 2014, Laird-Maddox *et al*. demonstrated pre-population of diabetes eCRFs in a Cerner EHR extension of the IHE RFD standard [38]. This technical solution was built within the Cerner Millennium EHR and Discovere research data capture system [38]. Discovere is a separate, web-based platform that can be used independently of Millennium and supports traditional electronic case report form data capture [38]. The RFD-based technical solution enabled electronic transmission of relevant data from the Millennium EHR to Discovere [38]. The technical solution leveraged an EHR-generated Continuity of Care Document (CCD) containing the most recently populated values for the study data elements [38]. The pilot reported minimal interruption of the EHR session

and available data flow from the EHR to the study eCRF without manual reentry [38]. The investigators claimed improved data quality and reduced data collection time, but the results were not quantified [38].

In 2015, Lencioni *et al.* reported on EHR-to-Adverse Event Reporting System (AERS) integration [39]. At the University of Arkansas for Medical Sciences (UAMS), AERS was implemented and interfaced with the Epic EHR to leverage routinely collected clinical data and automate detection of detectable adverse events (AEs) [39]. The system integration software was developed to provide systematic surveillance and detection of adverse events knowable from the health record including (1) lab related adverse events that are auto generated based on study participants' lab results and (2) unscheduled visits. The system uses MirthConnect's web service, HL7 messages, and the IHE Retrieve Process for Execution (RPE) integration profile [39]. Implementation of this system was associated with a reduction in sponsor generated AE-related queries, and a staff-estimated 75% increase in lab-based AE reporting. Data quality was not assessed. The system remains in use today at UAMS and has been followed by additional ongoing EHR-to-Research system integration activities. This work demonstrates the direct integration of an EHR with clinical research systems. However, this solution was implemented at a single site and assessed only two endpoints based on staff perceptions.

Nordo *et al*. reported development, installation, and evaluation of standards-based EHR-to-eCRF software in an ongoing single site for an OB/GYN registry [28]. The technical solution was based on the IHE RFD integration profile. The evaluation study compared eSource to non-eSource (usual practice of manual medical record abstraction) data capture. The overall average data capture time was reduced with eSource versus non-eSource methods (difference, 151 sec. per case; eSource, 1603 sec.; non-eSource, 1754 sec.; $p= 0.051$) [28]. The average data capture time for the demographic data was reduced (difference, 79 sec. per case; eSource, 133 sec.; non-eSource, 213 sec.; $p < 0.001$) [28]. This represents a 37% time reduction (95% confidence interval 27% to 47%). eSourced data field transcription errors were also reduced (eSource, 0%; non-eSource, 9%) [28]. Though the study promisingly concluded that the use of eSource versus traditional data transcription was associated with a significant reduction in data entry time and data quality errors [28], the results lack generalizability due to implementation at only one site.

4.2 Multi-Site, Multi-EHR Implementations

Several authors report on aspects of the collaborative EHR for Clinical Research (EHR4CR) initiative [31,34,40-43]. Using a different architecture than RFD, the RE-USE (Retrieving EHR Useful data for Secondary Exploitation) project leveraged a semantic mapping process to match EHR data to elements of the electronic case report form for research [31]. In a pilot conducted at George Pompidou hospital in France, they found that 13.4% of the study data elements were present in EHR and available for pre-population of study CRFs [31,34]. In the same pilot precision, positive predictive value, ranged from 62%-84% and sensitivity ranged from 31% - 84% [31]. Beresniak (2017) estimated cost benefit of the EHR4CR platform for the three use cases (trial feasibility assessment at sites, subject recruitment and data collection) including 50k–500k € for EHR4CR platform service provider fees using experts rating hypothetical studies as part of pre-commercialization assessment [41]. The EHR4CR European Pilot went further than a single facility and demonstrated installation of the software in university hospitals

in five European countries. However, the EHR4CR platform has not yet been tested in a randomized clinical trial [42,44].

4.3 Multi-Site, Multi-EHR Implementations as part of Ongoing Clinical Trial

Ethier *et al.* reported results from the European FP7 TRANSFoRm project towards developing an infrastructure for a Learning Health System in European Primary Care (www.transformproject.eu); a major work stream of the project was directed at developing eSource connectivity for randomized controlled trials [30]. FP7 refers to the European Union's Seventh Framework Program for research, technological development and demonstration. Similar to EHR4CR, the TRANSFoRm scope of functionality was broader than the aforementioned attempts at EHR-to-eCRF integration and included automated eligibility screening and support for recruitment, pre-population of study CRFs, study data document archival in the EHR, and mobile-device capture of Patient Reported Outcomes [30]. The technical approach extended CDISC's ODM so as to send the data queries to the EHR and to then prepopulate the CRF with 26 extracted data elements [30,45]. The TRANSFoRm eSource method and tools were implemented as middleware between the EHR and the EDC system. However, the approach required collaboration from each of the five EHR vendors to implement [30]. The study compared TRANSFoRm to standard methods for the outcome of clinical trial recruitment in primary care [30]. Although this study failed to detect a significant difference in overall or weekly recruitment rates, the secondary outcome of data completion rate did show a significant treatment-related difference. Unfortunately, data quality and site effort were not evaluated. Nonetheless, the TRANSFoRm project did demonstrate that implementation of EHR-to-EDC integration can occur within an RCT's start-up timeline.

4.4 Limitations

We acknowledge the inherent limitations of this review. Although we attempted an exhaustive search of the literature using robust biomedical databases, manuscripts meeting our inclusion criteria were difficult to find, and we understand that some relevant manuscripts may have been missed. Further, while we leveraged the efforts of two independent reviewers to screen the titles and abstracts, only a single reviewer screened the full-text articles. We realize that our methods would have been strengthened by having double-review throughout.

4.5 Future Research

As part of an existing effort to expand on the work of Nordo *et al*., we – in collaboration with several academic, industry, and government partners – are currently working to convert existing EHR-to-eCRF software from the RFD standard to the HL7 Fast Healthcare Interoperability Resources (FHIR) standards to support EHR- and EDC-agnostic implementation. This approach would provide a standards-based tool for semi-automated, near-real-time direct EHR data extraction for use in multi-center clinical studies that builds on strengths and overcomes weaknesses prior approaches, specifically targeting generalizability and scalability.

5. Conclusion

The long-sought, semi-automated extraction and direct use of EHR data in clinical trials is within reach. As described above, solutions have been developed, evaluated and improved. However, generalizability, scalability, and effectiveness towards increasing data quality and efficiency in multicenter studies has not been demonstrated. Therefore, additional studies are needed to address the critical barriers to progress in streamlining clinical trials by probing these unanswered questions, furthering the development of critical methods and tools, and directly testing their impact on data quality, collection cost, collection time, and site recruitment. The answers to these cost, quality, time, and socio-technical implementation issues will inform the true value of EHR-to-EDC eSource data collection towards streamlining clinical studies.

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Appendix

Appendix 1. Summary of the Literature (S = single-institution / -EHR, M = multi-institution / -EHR)

Source	Institution	EHR	Within Ongoing Trial?	Standards	Findings / Limitations
Gersing K, et al. (2003)	S	S	N	N/A	Designed a behavioral health EMR that integrated research and care.
Murphy EC, et al. (2007)	S	S	N	N/A	Demonstrated custom-built screens in an EHR system that included capturing research-related data, which were later extracted from the EHR database.
Kush MG, et al. (2007)	S	S	Y	HL7 CDA, CDISC ODM	STARBRITE Demonstration Project: demonstrated the feasibility of a single capture of clinical data with subsequent use in patient care and a clinical trial. Due to the delayed finalization of clinical documentation at the institution, initial data capture occurred in the study CRF.
Kim D, et al. (2008)	M	M	N	N/A	Distilled 42 distinct ways (14 use case categories) in which direct use of EHR data might improve clinical trials. Five use case categories involved the conduct of prospective clinical studies – the primary interest of this review is the clinical trial data collection use case.
Kiechle M, et al. (2009)	S	S	Y	HL7, CDISC ODM	The Munich Project: Leveraged HL7 messages from the EHR and, upon human review, data was transferred to the EDC system. Demonstrated a statistically significant reduction in time for data collection activities; resulting in an almost five-hour reduction in data collection time.
El Fadly A, et al. (2011)	S	S	N	HL7 CDA, IHE RFD, CDISC ODM	RE-USE Project: leveraged a semantic mapping process to match EHR data to elements of the eCRF for research. The RE-USE approach demonstrated a reduction in redundant data entry and improvement in data quality and processing speed.
Laird-Maddox M, et al. (2014)	S	S	N	HL7 CCD, IHE RFD	Cerner Discovere: demonstrated pre-population of diabetes eCRFs in a Cerner EHR extension of the IHE RFD standard. The investigators claimed improved data quality and reduced data collection time, but the results were not quantified.

Beresniak A, et al. (2014, 2016)	M	M	N	HL7 RIM, EHR4CR	EHR4CR European Pilot: report on aspects of the collaborative EHR4CR initiative. Estimated cost benefit as part of pre-commercialization assessment. The EHR4CR European Pilot went further than a single facility and demonstrated installation of the software in university hospitals in five European countries. However, the EHR4CR platform has not yet been tested in a RCT.
Doods J, et al. (2014)	M	M	N	HL7 RIM, EHR4CR	
De Moor G, et al. (2015)	M	M	N	HL7 RIM, EHR4CR	
Dupont D, et al. (2017)	M	M	N	HL7 RIM, EHR4CR	
Lencioni A, et al. (2015)	S	S	Y	HL7, IHE RFD	AERS: EHR-to-Adverse Event Reporting System integration with the EHR to automate detection of detectable Adverse Events. The system uses MirthConnect's web service, HL7 messages, and the IHE RPE integration profile. Associated with a reduction in sponsor generated AE-related queries, and a staff-estimated 75% increase in lab-based AE reporting. Data quality was not assessed. Implemented at a single site and assessed only two endpoints based on staff perceptions.
Ethier JF, et al. (2017)	M	M	Y	CDISC ODM	European FP7 TRANSFoRm Project: developing eSource connectivity for randomized controlled trials. Formally evaluated using a mixed-methods study of TRANSFoRm as a nested cluster randomized trial embedded fully within an RCT. Failed to detect a significant difference in overall or weekly recruitment rates, but data completion rate did show a significant treatment-related difference. Data quality and site effort were not evaluated. Demonstrated that implementation of EHR-to-EDC integration can occur within an RCT's start-up timeline.
Nordo AH, et al. (2017)	S	S	N	IHE RFD	Development, installation, and evaluation of standards-based EHR-to-eCRF software in an ongoing single site for an OB/GYN registry; based on the IHE RFD integration profile. Compared eSource to non-eSource data capture. The overall average data capture time was reduced (difference, 151 sec. per case; eSource, 1603 sec.; non-eSource, 1754 sec.; p= 0.051). eSourced data field transcription errors were also reduced (eSource, 0%; non-eSource, 9%). Results lack generalizability due to implementation at only one site.