eSource Part 4
Regulators

A Topic Brief Series on eSource:

SCDM eSource

Society for Clinical Data Management (SCDM)

eSource Implementation Consortium

Playbook 4: A personal regulatory view
Version 1 (September 2023)

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Abstract

Clinical research is in the midst of a digital transformation, with the emergence of eSource data promising to accelerate drug development timelines, enhance patient centricity, and unlock previously unseen insights. While much has been written on the rationale for eSource approaches, practical advice on their implementation has been less widely available. As the world's leading advocate for the discipline of clinical data management, the Society for Clinical Data Management (SCDM) is in a unique position to fill this knowledge gap. To achieve this aim, the group has produced a series of podcasts in which leading experts from across the clinical research ecosystem share their case studies and practical advice on moving eSource from theory into practice. We then distilled their learnings into four playbooks, each from the standpoint of one of the main stakeholder groups: CROs and vendors, pharma, regulators, and academia/sites. This paper focuses on a regulatory perspective.

Methodology

The eSource Implementation Consortium is publishing an eSource topic briefs series intended to serve as orientation guides on eSource which are contributing directly or indirectly to the evolution of Clinical Data Management (CDM) into Clinical Data Science (CDS). Due to the absence of a comprehensive and authoritative literature base regarding the wide implementation of eSource within the Drug Development industry, this content was gathered from industry leaders through an opinion-based methodology. As eSource implementation mature, and technology evolves, the Consortium anticipates that literature on this topic will blossom.

Podcast interviewees were selected for their eSource expertise according to SCDM Board recommendations and/or were members of the SCDM eSource Implementation Consortium. Efforts to reduce bias included using a standard set of questions, based on input from the SCDM eSource Implementation Consortium and conducting interviews with 17 contributors from four different perspectives. Contributors were asked to share their thoughts on barriers to eSource adoption and implementation from their personal experiences of the approach, and to provide case studies.

Post-podcast recording, the recordings were grouped into four perspectives: CROs and vendors, pharma, regulators, and academia/sites. The transcripts were reviewed to identify key themes, which were then summarized to form a narrative, playbook-style report. Podcast contributors were asked to review the drafted content to ensure their viewpoints had been represented faithfully.

Interviewees: *

Name	Job title / Organization	Sector
Jonathan Andrus	President and COO at CRIO, and SCDM Treasurer	Vendor/CRO
Alex Crawford	Director of Decentralized Clinical Trial Products, DCT Operations, ICON	Vendor/ CRO
Kristen Harnack	Director of Solutions Consulting, Castor	Vendor/CRO
MD Naqib Alam Ansari	Senior Manager, Clinical Data Strategy and Operations, AbbVie R&D	Pharma
Magda Jaskowska, PhD	Global Director/Leader Oncology, Data Strategy and Management, GSK	Pharma

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Lauren McCabe	Associate Director, Clinical Data Science, Pfizer	Pharma
Muzafar Mirza	Senior Group Lead, Clinical Data Sciences, Pfizer	Pharma
Joseph Angiolelli	Director, Information Management/Clinical Trial Solutions, Pfizer	Pharma
Peter Casteleyn	Director, Data Collection Solutions-EHR, Janssen R&D	Pharma
Rakesh Maniar	Executive Director and Head of eClinical Technologies, Global Clinical Trials Operations– Global Data Management and Standards, Merck & Co., Inc.	Pharma
Nadir Ammour, DDS	Global Lead for external engagement, Transformation & Performance Office, Clinical Science & Operations / Development, Sanofi R&D	Pharma
Mitra Rocca	Senior Medical Informatician, FDA	Regulatory
Jeff Stein	President of Stamford Therapeutics Consortium	Sites/academia
Michael Buckley	Associate Director of Product Management, Clinical Research Informatics and Technology, Memorial Sloan Kettering Cancer Center	Sites/academia
Elena Christofides, MD	Owner, Endocrinology Research Associates	Sites/academia
Cory Ennis	Director of Information Technology- Engagement and Assistant Dean for Research Systems, Duke University School of Medicine's Office of Academic Solutions and Information Systems	Sites/academia
Denise Snyder	Associate Dean for Clinical Research, Duke University School of Medicine Office of Clinical Research	Sites/academia

* All interviewees consented to use of their quotes. All information included in this report has been reproduced with the permission of the interviewees and the SCDM.

Introduction

Clinical research is in the midst of a digital transformation, with the emergence of eSource data promising to accelerate drug development timelines, enhance patient centricity, enhance sponsor, and site efficiencies, and unlock previously unseen insights. eSource refers to the direct collection (entry or acquisition) of clinical data into an eSource system from site staff, clinical trial participants, or care givers. It can include direct from device, such as wearables or sensors, direct from clinical trial participants or clinician/site staff, such as eCOA, or direct from an electronic health record (EHR).[1] The approach reduces the need for source data verification (SDV), minimizing the need for transcription and providing real-time guidance on illogical or inconsistent data at the point of collection. If implemented correctly and in compliance with ICH-GCP, it can reduce site burden, boost patient centricity, and improve data quality.[2]

As the industry moves from the "why" to the "how" of eSource, however, it is clear that adoption can sometimes present just as many challenges as it does opportunities. The new paradigm often requires the integration of disparate data sets, using multiple technologies, and

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redesigning existing work and data flows, for example. While much has been written on the rationale for eSource approaches, practical advice on their implementation has been less widely available.[3] As the world's leading advocate for the discipline of clinical data management, the Society for Clinical Data Management (SCDM) is in a unique position to fill this knowledge gap.

SCDM eSource Implementation Consortium

SCDM is one of several industry bodies backing the use of eSource, which offers a wide range of benefits. The consensus is that it can "improve protocol design and clinical trial participant recruitment, modernize, and streamline data collection, monitoring and reporting"[2], thereby improving healthcare and outcomes. It can enhance "site and participant experience, reduce data entry errors, minimize the 'burden of source data verification', and 'facilitate' the use of 'risk-based monitoring (RBM)', as well as enable real-time data review and generate the outcomes-based evidence sponsors need to demonstrate the value of their products"[2].

Despite the well-documented advantages and wide availability of eSource tools, challenges around implementation mean adoption has been slow. SCDM eSource Implementation Consortium, which includes representatives of leading biopharmaceutical companies, academic medical centers, regulatory bodies, and healthcare technology providers, was established in 2017 to further the adoption of eSource approaches.[4] As part of that work, the group has produced a series of podcasts in which leading experts from across the clinical research ecosystem share their practical advice on moving eSource from theory into practice. We have also distilled their learnings into an eSource Topic Brief series of four playbooks, each from the standpoint of one of the main stakeholder groups: CROs and vendors, pharma, regulators, and academia/sites.

Playbook 4: A personal regulatory view

As part of the Playbook project, we spoke to Mitra Rocca, Senior Medical Informatician at the United States Food and Drug Administration (FDA). Mitra has been working with various forms of eSource data since 2006.

Typical challenges to adoption

There are various challenges to the adoption of eSource, and they tend to center around:

- lack of standardization of data
- lack of interoperability among various health IT systems within one organization and across healthcare delivery organizations
- lack of linkage between various eSource data, such as electronic health records (EHR) and claim data

Case study: Data harmonization for ease of analysis

Proposition: The Common Data Model Harmonization (CDMH) project aims to harmonize four common data models to generate real-world evidence.

The challenge: Mapping EHR data from Health Level 7 (HL7) Fast Healthcare Interoperability Resources (FHIR) format to CDISC Study Data Tabulation Model (SDTM) to enable analyses is challenging. One of our challenges was to map EHR data from HL7 FHIR to CDISC SDTM format in order to be able to analyze the data.

The solution: The ideal solution would be tools that enable researchers to analyze HL7 FHIR datasets directly.

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Data integration

Rocca outlined the Source Data Capture from Electronic Health Records (EHRs): Using Standardized Clinical Research Data (OneSource) project.[5] The FDA and University of California, San Francisco (UCSF) collaboration aims "to develop methods and tools to automate the flow of structured EHR data into external clinical research systems"[6]. The goal is to "reduce operating costs, save time, and improve data quality."[7] It integrates data according to HL7 FHIR standard to enable the auto-population of electronic case report forms (eCRF) from EHRs. The site staff are in control of the data transfer. They are able to trigger auto-population of eCRFs from within the EHR user interface via a SMART on FHIR app. The system automatically filters the data transfer to limit to only records that are needed for the clinical trial. The OneSource infrastructure is currently being applied to I-SPY 2 breast cancer trial and COVID-19 drug studies.

Data cleaning

The OneSource project team has developed validation checks that assess the reasonability of the data within a patient series or across all patients in the study. For example, for a lab result that may have multiple LOINC code identifiers that vary across sites, validation routines were conducted prior to site implementation to ensure the correct assay result was pulled, said Rocca, adding that periodic verification was conducted to confirm no changes are made at the site/EHR level for data mappings. With relation to the Common Data Model Harmonization or CDMH project, CDISC validation rules are applied to the datasets.

Standardization and terminology

Rocca pointed to a number of key gaps in data standardization and terminology. For example, United States Core Data for Interoperability (USCDI), a subset of FHIR adopted as a standard in the Office of the National Coordinator for Health Information Technology (ONC) Cures Act Final Rule[8] is missing clinical research data elements. Other areas in need of improvement relate to controlled terminologies. Healthcare providers in the US, for example, use International Classification of Diseases, Tenth Revision (ICD-10), and Systematized Nomenclature of Medicine: Clinical Terms (SNOMED-CT). However, these terminologies need to be harmonized with the Medical Dictionary for Regulatory Activities (MedDRA), which regulators, including the FDA and European Medicines Agency (EMA), require.

Data flow

The OneSource project uses both HL7 FHIR and CDISC Operational Data Model (ODM) standards to move the data. Rocca explained: "Site staff are in control of the data transfer, triggering auto-population of eCRFs from within the EHR user interface using the SMART on FHIR app. The system automatically limits data transfer to those records that are needed for the clinical trial at hand."

Use of EHRs in clinical research: Post Podcast update

Additional question: Regarding the expectations for a sponsor's due diligence concerning how sponsors need to qualify an EHR system in order to use the information from it, additional questions might be - is an ONC-certified EHR required? what is required for non-certified EHRs?

Post Podcast update: Per Mitra, the "FDA recognizes the importance of data from foreign studies to support safety and efficacy claims for medical products and may accept data from clinical studies conducted outside the United States. EHR systems not certified by ONC, including EHR systems at foreign clinical sites, can provide adequate data to inform FDA's regulatory decisions provided that adequate controls are in place to ensure the confidentiality, integrity, and security of

data. Specifically, for EHR systems not certified by ONC, sponsors should consider whether such systems have the following privacy and security controls in place to ensure that the confidentiality, integrity, and security of data are preserved"[9]:

1. "Policies and processes for the use of EHR systems at the clinical investigation site are in place, and there are appropriate security measures employed to protect the study data.
2. Access to electronic systems is limited to authorized users.
3. Authors of records are identifiable.
4. Audit trails are available to track changes to data.
5. Records are available and retained for FDA inspection for as long as the records are required by applicable regulations."[9]

"Sponsors should consider these factors when determining the suitability of EHR systems not certified by ONC for use in clinical investigations. If the clinical investigation site is using a system that does not contain the adequate controls previously described in the bulleted items, sponsors should consider the risks of employing such systems (e.g., the potential harm to research subjects, patient privacy rights, and data integrity of the clinical investigation and its regulatory implications). The following information may be helpful to sponsors to determine the suitability of EHR systems not certified by ONC".[9]

- "Any EHR system certification information from other authorizing bodies outside the United States, including information about aspects of the EHR system that the authorizing body evaluated when certifying the EHR system."[9]
- "Feature and product-specification information from the EHR system vendor. Sponsors should consult with the relevant FDA review divisions if any issues or challenges with the EHR system are identified."[9]

For EHRs certified by ONC, an ONC-certified system could only ensure numbered bullets 2, 3, and 4. Under section V.A of the guidance (use of Health Information Technology certified by ONC), FDA encourages the use of certified EHR systems together with appropriate policies and procedures for their use. Records must be available for inspection in Section VI (e.g., viewable in the EHR or certified copies). So, in addition to ONC certification, bullets 1 and 5 in the list above are also important in the sponsor's due diligence assessment of the ONC-certified EHR system to ensure data quality and integrity.

The future of eSource

Rocca believes data fields required for clinical trials should not only be added to EHR systems as a matter of course, but that they should also become part of the EHR certification program in the US. "There is also a need to enhance standards for digital health technologies so we can integrate them with data from other eSources, such as EHR," she added.

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