A Topic Brief Series on eSource

Society for Clinical Data Management (SCDM)

eSource Implementation Consortium

Playbook 2: Taking a sites'-eye view

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No conflicts of interest

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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 the academia/site's 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 matures, 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

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 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 2: Taking a sites'-eye view

As part of the Playbook project, representatives from sites and academia shared their experiences:

- Jeff Stein, President of Stamford Therapeutics Consortium, has a wealth of experience in this area, with his organization becoming a beta user of the first available site-focused eSource platform back in 2017
- Michael Buckley, Associate Director of Product Management at Memorial Sloan Kettering Cancer Center (MSKCC), has been working with eSource and electronic data capture (EDC) since 2017
- Dr Elena Christofides, practices endocrinology in Columbus, Ohio, and runs the independent research facility, Endocrinology Research Associates. She has been working with eSource for more than a decade
- Cory Ennis, Director of Information Technology and Assistant Dean for Research Systems at Dukes University School of Medicine's Office of Academic Solutions and Information Systems (OASIS), where he focuses on the creation of a central intake for all research technology needs
- Denise Snyder, Associate Dean for Clinical Research at the Duke University School of Medicine Office of Clinical Research, a central support office of expertise in coverage analysis, study logistics, data management, regulatory oversight, workforce innovation, and guidance for clinical research operations.

Typical challenges to adoption

For sites, typical challenges tend to center around change management and solution/ platform overload. All our contributors highlighted how important it was to note that eSource

adoption requires detailed, solution-specific amendments to processes and workflows. At a practical level, different sponsors are asking sites to work with different eSource platforms, all of which offer similar functionality, but must be absorbed into routine workflows individually. Each will require time- and resource-intensive compliance, data privacy, security clearance, and staff training procedures. This can drive up the cost of eSource adoption, frustrate sites and clinicians, and create resistance to change.

> *"Part of our struggle with the process has been that everybody has something a little bit different. We just do not have the resources to implement a different system for every single project, so the more we can develop a uniform way of doing it, the easier it will be for sites to adopt."* Snyder.

One of the benefits of eSource is that it allows for more robust oversight of data quality by time and date stamping data entry. However, the requirement for real-time data input runs counter to how investigators in the past were used to transcribing data at a time that suited their competing clinical practice responsibilities. Change management is key to moving to a new workflow paradigm for all stakeholders.

"I would encourage sponsors to pay attention to the systems sites are adopting themselves, and understand the reasons for that. I selected a system with a single interface for virtually all of the functions we need to perform our business. To me, that's the ideal way for a research site to be functioning. Sponsors need to understand when they start introducing things that disrupt that workflow, it makes it harder and harder for the site staff to do what they have to do. At the end of the day, that compromises the quality of the work that we do," said Stein.

Buy in

Securing buy-in from site teams and investigators is the first step to successful implementation. Doing so relies on demonstrating both the benefits of the approach, and a commitment from an organization's leaders. Rollout should be performed in digestible stages that allow teams to absorb and understand the full context and capabilities of each part of the system before moving onto the next. Greater universality in the systems deployed and allowing sites a seat at the table when adopting eSource, i.e., allowing sites to choose their own tools or have input to which ones are used, could help to streamline site adoption.

"One of the biggest challenges is staying on top of the technology as it evolves: no technology is static. All organizations need to have a subject matter expert, someone who knows more about the systems than anyone else and who employees can go to with issues, especially as new functionality is being rolled out," said Stein.

Existing evidence base

An eSource readiness survey of 61 "principal investigators, clinical research coordinators, and chief research information officers at Pediatric Trial Network sites" was conducted between January 2020 and June 2021.[5] "While most organizations used some electronic health records research functions"[5], just "21% of sites were using Fast Healthcare Interoperability Resources (FHIR) standards to exchange patient data with other institutions"[5]. The authors concluded technical tools and knowledge were not the only barriers to eSource readiness among research sites. "While computer capabilities are important, organizational priorities, such as clinical care versus research, availability of a research IT group to support EHR eSource studies, and the site's previous use of EHR clinical research functions, are equally important,"[5] they wrote, mirroring the perspectives of our podcast interviewees.

Data integration

Our four experts gave differing viewpoints on the issue of data integration. At a research-only site, data may be entered directly into a site-focused eSource system, according to the parameters of the specific study. As such, data is captured in a structured format and additional access is not usually required. Integrating data from various eSources will often present challenges to sites and other stakeholders, such as vendors, sponsors, or technology developers, who are often unaware of the full extent of the burden.

Case study: Integrating disparate eSources

A number of third-party apps and devices, including an eDiary, a blinded continuous glucose meter (CGM) and a non-blinded CGM, were deployed in an insulin trial.

There was, however, a lack of integration:

- between the apps, meaning patients were asked to use separate devices for the eDiary and CGM elements, and
- between the devices and the EDC platform

In addition, none of the third-party technology providers were able to provide the site with tech support for the use of their products in a clinical trial.

Within months of study initiation, this had led to more than 1,000 open queries related to protocol deviations. In addition, the first two patients had dropped out of the trial, frustrated with the incompatibility of the devices. They also felt the financial compensation offered by the sponsor was not adequate to cover the time spent dealing with the malfunctions.

Such issues can be prevented by:

- Sponsors working directly with the manufacturers of the apps and devices they wish to deploy, rather than with third party platform providers who do not have access to the necessary software
- Sponsors recognizing the additional site and patient time needed to implement complex eSource trial designs, and remunerating them accordingly

> *"We're actively working with technology vendors that are directly managing integrations between sites and sponsor EDCs. Since sponsors are often comfortable with vendor relationships as the middle layer between them and the site, we feel this partnership will allow greater 'stickiness' and enable uptake and scaling."* Buckley.

EHR to EDC integration

Integrating EHR data into EDC systems can be challenging, our site/academia representatives told us. EHRs may include irrelevant or inaccurate information on diagnosis (e.g., a 'rule out' diagnosis), medication (e.g., prescriptions not filled or not taken by patients), and other interventions for various reasons, not least because they are working continually updated systems designed to primarily satisfy coding and billing/reimbursement requirements. As such, there is no way to simply "copy and paste" the data directly in a way that will meet the exacting, precise requirements of clinical trials.

At Christofides' organization, they overcome this challenge by mounting a joint review by nurses and research coordinators. It involves face-to-face conversations with patients to confirm

data points and obtaining pharmacy records to check prescribed medications. This information is then cross-referenced with inclusion/exclusion criteria.

> *"CROs and sponsors often want direct EHR to EDC data because they think they can save money, but it actually costs us more because we have to spend more time interviewing the patient."* Christofides.

Data cleaning

Our conversations with contributors found that sites tend to pull data direct from the source, but some data types will require data management or adjudication.

Aligning the data to a data model standard like HL7's Fast Healthcare Interoperability Resources (FHIR) is helpful in addressing the data completeness issues often encountered with real world data, for example, but the approach is far from ideal. Data pulled from EHRs will not directly map to MedDRA codes in EDC, and additional work is needed to track from one to the other. In addition, EHRs may contain additional time points (e.g., multiple Blood Pressure readings), potentially inaccurate or even irrelevant information that, while useful in the healthcare setting, is not precise enough to be used in research. Most centers will review patient records and make adjustments, or corrections before pulling the data, aka 'human in the loop' processes, to ensure it is suitable.

It is a responsibility that often falls on the sites, but missing data can have an extremely negative impact on submissions, with sites deemed to have incomplete or "unclean" datasets increasingly being removed from analysis by regulators such as the FDA. As such, sponsors will benefit from taking more of an active role in supporting sites to develop robust processes.

In terms of ongoing data cleaning, site eSource systems tend to contain an internal query functionality that enables monitors or quality assessors to raise queries with investigators.

Standardization and terminology

While much work has and continues to be done in creating data standards for use in clinical trials, there remain many gaps. In some quarters, moves are being made to adopt the Cybersecurity Maturity Model Certification (CMMC) framework and/or the upcoming National Institutes for Health (NIH) data standards.

> *"FHIR was designed to improve our diagnostic abilities, not our precision research abilities."* Christofides.

FHIR, a set of resources designed to facilitate greater interoperability, appears to receive the most attention. However, it has limitations, not least that its terms do not tend to be precise enough for use in research.

> *"FHIR doesn't cover every use case or scenario, but it is flexible enough to allow extensions. So far, the area we have found with the most gaps is the tumor measurement response domain."* Buckley.

Ennis also pointed to internal gas in standards, whereby different teams in different parts of the faculty will store data in different ways.

> *"As eSource becomes centrally adopted, I hope that will drive the more wide-scale adoption of data standards."* Ennis.

Data flow

Transferring data from sites to sponsor EDCs or data warehouses largely remains a manual process with little standardization, our experts explained. Data portals, which allow sponsors to log on and export their data in a FHIR format, are one option being used.

> *"When using EHR to EDC systems, it is key to have a middleware-facilitated data feedback loop when moving and reviewing data."* Snyder.

Case study: Integration layers

MSKCC has developed ingestion layers to move data from site-focused systems into the eCRF and relies on sponsors to build these layers out. How this is approached depends on the use case. For investigator-initiated trials, extract, transform, and load (ETL) methods move data from a central data warehouse into another internal location for easy access. For sponsor EDC systems, the team use a Chrome extension. They have also developed a data product, CT Data Hub, to help populate forms within United States national registries.

There is a need to build standardization in this space, and including sites in discussions would benefit all parties.

> *"We want to participate in clinical trials and our patients want to be a part of the future of creating and developing new methods and new medications. As a clinician, it's very distressing to not have a seat at the table when these methods are being created, because it will ultimately be detrimental to the movement to more efficient, more cost-effective clinical trials and more valuable data collection."* Christofides.

The future of eSource

Our site/academia representatives gave us their views on the future of eSource and what needs to be done to fulfill the potential of this new framework. All noted the importance of cross-sector working, and many said they expected to see more open systems that allowed for an agnostic approach.

"There are a lot of vendors in this space, and the reality is that sites just do not have the resources to implement different systems for different sponsors," said Ennis, adding that using common data standards, like FHIR, would allow sites to integrate their EHRs with eSource platforms and go some way to achieving the aim of universal adoption. Stein agreed and said that he hoped sponsors would start to involve sites more in solution selection processes. "Currently, sponsors are not paying attention to the technology sites are adopting on their own. Rather, they are selecting solutions and, if not insisting then at least suggesting that sites use them. It is disruptive to most site workflows. It means sites having to work with multiple systems for each sponsor that they're working with, which becomes unmanageable for staff," he said. "It would be much better if sponsors looked at what sites are already using, and asking how they can work with those systems to accommodate their end objectives."

Buckley also said that agnostic approaches were the key to advancing eSource, adding that resource constraints and data privacy concerns meant the industry was "stuck in a bespoke point-to-point solution era." "There are solutions out there that successfully manage business-to-business integrations and include translation and mapping engines. We're starting to test and investigate these, alongside sponsors and regulatory agencies, to ensure they meet everybody's needs, but they could be that 'middle layer' to help manage business-to-business transport of the data."

In the future, greater automation of data flow would enable immediate data transfer, minimizing data entry mistakes and providing sponsors with more timely access to safety data. This can only be achieved with cross-sector support, and by vendors opening their APIs to each other. "The next iteration of eSource is these systems being able to connect in an agnostic fashion. That's the direction I think we're going, but it's going to take some time to get there," said Stein.

According to Christofides, CROs, sponsors, and regulators also need to recognize the value of data already being collected through things like fitness trackers and apps or BYOD (bring your own device). "Patients are already measuring their data, and clinicians are already collecting it," she said, adding that data from these sources can be scrubbed, anonymized, and put into a format suitable for review in a research setting. "It would be brilliant if we were able to talk to the manufacturers making these products and develop the capability to use the data, much like 23andMe and Ancestry are already doing with genetic data."

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