The Long Road to eSource

Since the introduction of electronic diaries in the early 2000s, eSource has provided an excellent opportunity to not only streamline clinical research, but increase data quality and trustworthiness

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Streamlining clinical research, particularly data acquisition, through the use of technology dates back to the 1990s with 'remote data entry', which was quickly renamed 'electronic data capture' (EDC) to reflect that data were being entered at investigative sites that were not 'remote', but rather the actual source of the data. While EDC technologies slowly gained traction, regulators were faced with the challenge of translating regulations written for paper-based processes to the new world of EDC. 'The Final Rule for FDA Title 21, CFR Part 11: Electronic Records; Electronic Signatures' was released in 1997 and generated numerous industry presentations, scenarios, and discussions related to the implementation of this regulation (1). Topics addressed included detailed analyses of aspects such as the source of the data, who had control of the data at a given point in the process, closed vs open systems, validation requirements, and change control procedures to maintain an audit trail. The FDA had authority to inspect these systems, and they needed to develop methods and training so that auditors could review electronic audit trails and validation documents.

Soon after the advent of EDC, came electronic diaries (eDiaries) for entry of data by patients or research participants themselves. These proved to have advantages over paper diaries in that the technologies employed were capable of creating an automatic 'audit trail' by date- and time-stamping the entry of the information. The automatic capture of time/date information highlighted instances of noncompliance, such as completing diaries in the parking lot prior to a visit and even instances of pre-filling diaries or anticipating how one would feel prior to the scheduled visit or diary completion date. After hearing of these advantages directly from the eDiary technology vendors, a group of FDA representatives agreed that such technologies deserved their further attention. The goal was to identify how they could support adoption of these technologies while still adhering to the predicate rules and paper-oriented regulations, which would take some time to change. They asked that a nonprofit neutral organisation, the Clinical Data Interchange Standards Consortium (CDISC), organise a group to hear all industry perspectives on the use of 'eSource', which was defined as "data initially recorded in an electronic format" (2). In response to this request, CDISC formed a collaborative group to explore eSource data interchange (eSDI) in 2004. Over the next two years, this initiative investigated "the use of electronic technology in the context of existing regulations for the collection of eSource data (including that from eDiaries, electronic health records [EHR], EDC) in clinical trials for regulatory submission by leveraging the power of the CDISC standards, in particular the operational data model (ODM)".

The goal of the eSDI initiative was "to make it easier for physicians to conduct clinical research, collecting data only once in an industry standard format for multiple downstream uses, thereby improving data quality and patient safety".

The eSDI document included:

- An extensive review and analysis of the relevant existing regulations
- Twelve requirements for conducting regulated clinical research using eSource data collection in the context of existing regulations
- Five potential scenarios, three of which include the use of EHR systems, and associated benefits of standards
- An appendix on responsibilities of each of the various functional groups conducting clinical research
- A template for evaluating an eSource data collection process against the requirements
- A good practices checklist for investigators

The requirements identified by this eSDI body of work were included in the CDISC primer 'Introducing the CDISC standards: New efficiencies for medical research' and were cited verbatim (albeit grouped in a different order to align with specific topics) in the 2010 EMA publication 'Reflection paper on expectations for eSource data and data transcribed to electronic data collection tools in clinical trials' (see **Box Out 1**) (3).

The FDA followed suit by developing guidance documents on eSource and on the use of EHRs for clinical trials. Specifically, the 'Final Guidance on Electronic Source Data in Clinical Investigations', published in 2013, was intended by the FDA to "promote capturing source data in electronic form" and to assist "in ensuring the reliability, quality, integrity, and traceability of electronic source data" (4). In 2016, the FDA published a guidance document related to eSource, specifically involving use of EHRs in clinical research. After addressing numerous comments, the final document, 'Final Guidance for Industry: Use of Electronic Health Record Data in Clinical Investigations', was published in 2018 (5).

During the time these regulations and guidance documents were being developed, there were a number of initiatives to demonstrate, technically, how EHRs could be used for clinical research. These included the STARBRITE project at Duke University Medical Center and Duke Clinical Research Institute in the US, and in Europe, the TRANSFoRm project and IMI's EHR4CR (6-8).

The 12 eSDI requirements were also leveraged in the development of i) an interoperability specification (IS #158) through the Health IT (HIT) Standards Panel as an American National Standards Institute process for the use case of EHRs for research, and ii) an Integrating the Healthcare Enterprise (IHE) profile, Retrieve Form for Data Capture (IHE/RFD). In 2017, Nordo *et al* demonstrated the value of using eSource (EHRs) and RFD in clinical research, specifically citing metrics for improved quality and reduced resources (9-11).

In the US, the Office of the National Coordinator of Health IT was created along with an HIT Standards Committee and an HIT Policy Committee. Through these activities, a certification programme for EHRs has now been established.

Requirement 1: An instrument used to capture source data shall ensure that the data are captured as specified within the protocol

Requirement 2: Source data shall be accurate, legible, contemporaneous, original, attributable, complete, and consistent

Requirement 3: An audit trail shall be maintained as part of the source documents for the original creation and subsequent modification of all source data

Requirement 4: The storage of source documents shall provide for their ready retrieval

Requirement 5: The investigator shall maintain the original source document or a certified copy

Requirement 6: Source data shall only be modified with the knowledge and approval of the investigator

Requirement 7: Source documents and data shall be protected from destruction

Requirement 8: The source document shall allow for accurate copies to be made

Requirement 9: Source documents shall be protected against unauthorised access

Requirement 10: The sponsor shall not have exclusive control* of a source document

Requirement 11: The location of source documents and the associated source data shall be clearly identified at all points within the capture process

Requirement 12: When source data are copied, the process used shall ensure that the copy is an exact copy preserving all of the data and metadata of the original

**Control: the ability to decide when source data are created, amended, viewed, or copied*

Box Out 1: eSource data interchange (eSDI) requirements

eSource Categories and Technologies

As the adoption of EHRs and the use of mobile apps increased, so did interest in leveraging such technologies directly for research purposes. The technologies that were referred to as eSource for clinical research began to cover a large and varied arena. TransCelerate conducted a landscape analysis, publishing Part I in 2016 and defining four categories for eSource. These four categories are: EHR/EMR,

devices and apps (used by non-site personnel and including smart phones, tablets, wearables, and sensors), non-CRFs (e.g., laboratory results), and direct data capture (DDC). DDC "includes direct entry of clinical data by site staff into a mobile application or EDC system" (12-13).

There are unique challenges, especially for the regulated industry, for each of these categories of eSource technologies:

EHRs
EHRs are challenging due to the disparate/proprietary nature of data formats and data models employed by the vendors, including the fact that these may be customised per hospital/site.

Devices and Apps
Devices and apps are particularly interesting, with the greatest challenges typically being related to data validation and accuracy, data formats that may not integrate with the rest of the trial data, and the sheer volume of data that are typically generated.

Non-CRF Data
Non-case report form (CRF) data probably presents the most immediate opportunity for integration with other clinical trial data since central laboratories have been practising eSource for many years now, integrating central lab data with research sponsor databases.

Direct Data Capture
Direct data capture has been an area where questions have recently been raised about data 'control' (who has ownership and control of, and responsibility for, the data), and vendors have been struggling to streamline processes and eliminate data transcription while adhering to global regulations. Specific to this category of eSource, the EMA recently responded to queries from the biopharmaceutical industry with a Qualification Opinion on eSource Direct Data Capture. This included drafting a response that was posted for industry comment, after which the final version was released in 2019 (14). While this publication resolved certain questions, it raised others. Additionally, it appears that there may be an opportunity for better global alignment among regulations and guidance on this topic.

A Proposed Fifth Category for eSource
A new business model could be focused on enabling community physicians to more readily participate in clinical research. Providing an infrastructure that facilitates research for a busy physician who is not part of a dedicated research site or major academic institution can increase the opportunities to offer research as a care option to more patients, increase the diversity of the patient population participating in clinical research, and ultimately, help close the learning healthcare loop to get better evidence into the hands of physicians more quickly, benefiting both research and patients.

Using EHR as an eSource tool may be very challenging for a number of reasons, including, but not limited to:

- Many different types of EHRs being used at community sites, with varied data models and data storage formats
- Most of the data needed for research are not already in the EHR (beyond screening and baseline data)
- Concern about study managers entering additional (research-specific) data directly into the EHRs, not to mention being able to access such data if entered

These issues could potentially be addressed by an eSource tool that is used routinely by site personnel to document eSource study data for all studies done by that site. It would use industry standards and would be controlled by the site, not the CRO or study sponsor. The resulting eSource document can be attached to the EHR record, continually accessible and controlled by the clinicians at the research site. The eSource data can then be transported (along with audit trail information) directly to a sponsor or CRO database, without requiring that site personnel re-enter these data into an EDC system.

Although the study source data collected through this eSource study documentation tool could electronically populate an EDC database or a clinical trial management system (CTMS), particularly those that are ODM certified, study managers are frequently requested to re-enter this source data into an EDC system, thus increasing the risk of transcription errors and resource needs.

When implemented as designed, this eSource study documentation tool (eSD) would enable streamlined processes:

- Collecting quality source data in a standard format from the start, supporting regulatory submissions with minimal mapping
- Accelerating access to management information and remote monitoring
- Reducing resource requirements
- Enabling a glidepath to use data directly from EHRs, especially when the HL7 fast healthcare interoperability resources (FHIR) standard has matured adequately to support research

Working with this solution satisfies immediate conditions for using EHRs in clinical research while also establishing a path to the direct capture and use of data from EHRs at such time in the future when the EHR data are sufficiently robust and standards are implemented to support clinical research.

eSource study documentation technology and the associated process are under the control of the investigator and his/her support staff and are part of their normal research procedure for all studies conducted at that site. Therefore, this type of

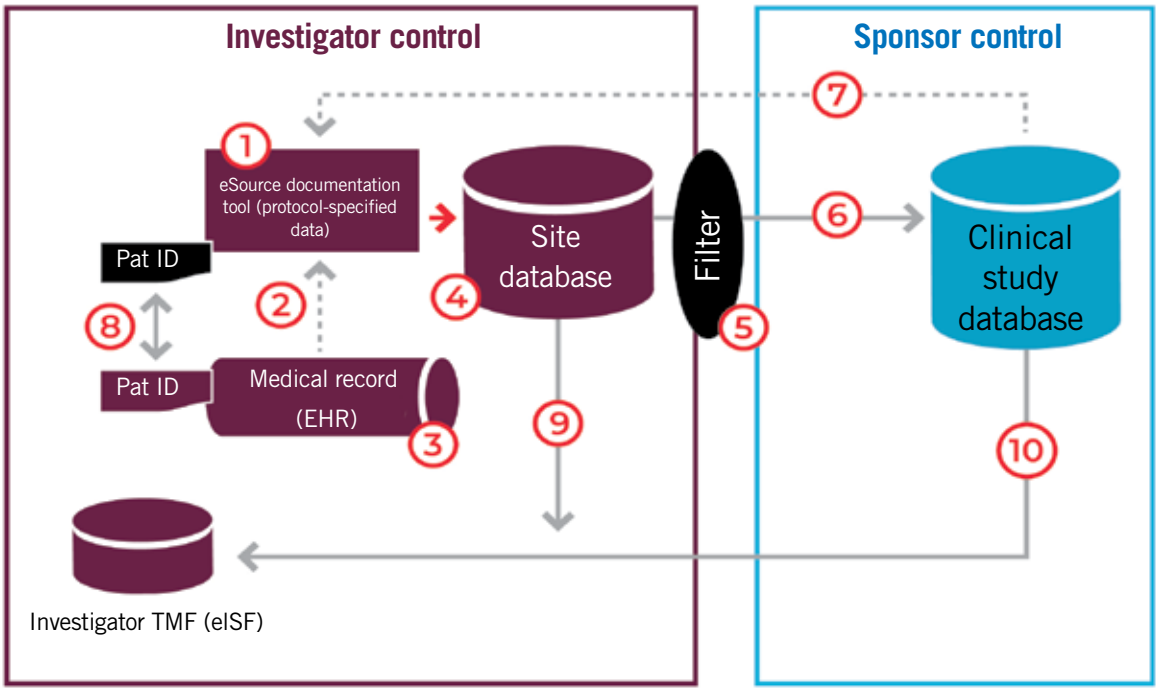
eSource differs from the typical DDC solutions, which are offered by a CRO or sponsor (or a vendor controlled by a CRO or sponsor) and used by the site only for the research study or studies done by that CRO or sponsor at that site. As described here, the eSource Study Documentation technology is not addressed in the EMA's published document on this topic nor in TransCelerate's four categories for eSource. Thus, it seems it may be appropriate to add a fifth eSource category in addition to the four currently described.

Figure 1 indicates a scenario for eSource documentation that is depicted as a revised version of the EMA's published scenarios for DDC.

Current Challenges to Broad eSource Adoption

While the clinical researchers continue to study, pilot, test, and re-pilot eSource methods, consideration should be given to how to best leverage new technology so that 'paper paths' are not simply repaved and that new processes are considered. Recent discussions around eSource have raised questions such as "Why EDC?" and "Why eCRFs?" Are these repaving old paper-based paths? Are eCRFs necessary if eSource is done properly at the site – the source of the data? Regulatory reviewers wish to review data that they can trace back to the site, and regulatory auditors must be able to trace the data from site to submission and/or the reverse; a robust and intact audit trail is essential for that. The more times data are transcribed, re-entered, or transported from system to system, the greater the opportunity for error and the greater the likelihood of disrupting the audit trail.

Another challenge is that certain organisations have still not adopted industry standards; they have their own proprietary standards for data collection and configure their EDC or eSource tools around these. This creates the need to map the by-patient data into standards that are required for regulatory submissions, while imposing excess burden on site personnel.



In this scenario, the eSD is the standard research process for the site personnel. (1) The eSD tool is set up to capture protocol-specific data for a given study, at the site by the investigator or study coordinator, in industry standard format, aligned with the site workflow, without constraints on the site and without undue burden on the site or the patient/study participant. (2) Any such data that are already in the EHR (e.g., prescreening data) must match the data in the eSD, and (3) the fact that the patient is in a clinical study is documented in the EHR. (4) All patient study data, audit trail information, CTMS information, and other management information are stored in the site database. (5) All personal health information and confidential data are filtered out and any data that are not study-specific or pseudonymised will not leave the site. (6) Only the protocol-specific patient data (pseudonymised) are sent to the clinical study database (or an EDC system, but this is considered an unnecessary step). (7) Queries on the data may be sent from the sponsor (or CRO) back to the site. (8) The patient ID in the records matches that in the eSD tool. (9) Copies of the site data can be maintained with the investigator trial master file (TMF) (eISF) although they are also continuously available to the site through their access to the site database. (10) Final study data (including all from the site database and additional study data [such as central lab data] are archived in the investigator TMF [eISF] for retention purposes).

Figure 1: Scenario – data entry at point of care (site-controlled eSource study documentation)

Another challenge alluded to previously relates to the fact that regulations and guidance around eSource are not yet globally consistent. However, when a company based in Europe conducts clinical trials in the US and Japan, their processes and methods must comply with FDA, EMA, and PMDA regulations. Efforts to harmonise regulations and guidance among regulatory agencies are very much appreciated; however, the understanding of how best to accommodate and regulate the various categories of eSource is still maturing, and there is more work to be done in this area.

Addressing eSource Challenges

In summary, to address the challenges to eSource success, the following recommendations are proposed.

First, focus on what we all want to achieve, i.e., source to submission (or publication, if the data are not collected in support of a regulatory submission), with as few transcriptions as possible while maintaining a robust audit trail for traceability and easing the burden on clinicians and site personnel.

Second, employ robust, global industry standards. Current standards that are mature, available, and relevant are CDISC ODM, CDASH, SDTM, and ADaM, associated with controlled terminology (NCI EVS) and therapeutic-area-specific standards; however, the standards may change with increased adoption of HL7 FHIR and the development of adequate FHIR resources to support research. Regardless, the need for semantic interoperability and support of audit trails will not change.

Finally, adhere to the basic requirements, which are essentially those that are associated with the 21 CFR11 regulation, while concentrating on the need to redesign old processes to appropriately leverage new technology in accordance with reengineering principles of looking at the problem through a new lens.

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