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eSource in the Age of Complexity

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When a study coordinator uses "eSource," he or she enters data into an electronic system like an electronic medical record or tablet computer, rather than onto paper. Data can then be transferred from the eSource system into the electronic case report (eCRF) system (also known as the electronic data capture (EDC) system), thus eliminating costly and error-prone step of transcribing data from paper source documents into eCRF forms.

eSource systems have been available for years, but their adoption has been slow, in part because study sponsors have been unwilling to incur the costs of acquiring the technology and reluctant to impose an eSource template onto sites, who they view as ultimately responsible for source data capture. Now, eSource has evolved to become a practical solution for sites, without intermediation by sponsors.

Benefits to Sites

eSource systems provide more than a place to enter data. They also provide three other essential functions: First, they can tell the study coordinator exactly which procedures to perform, how to perform them, and in what order. Second, they can explain why an eligibility criterion matters or why a procedure must be performed in a particular manner. Third, they can validate data in real-time, so if data is missing or out of range, the study coordinator can make any necessary corrections or confirmations immediately.

An eSource system should include the following features:

- Raise alerts based on how questions are answered
- Display previous data, e.g., which arm was previously used for blood pressure measurements
- Calculate averages and other formulae
- Employ branching logic so that certain questions appear based on previous answers

In theory, all of these functions can be performed without an eSource system, but the necessary materials and workflows add even more time-consuming and error-prone complexity. Electronic health record (EHR) systems, for example, are not optimized for clinical research, so modifying them for clinical research can require extensive and costly customizations.

eSource offers sites five practical benefits:

- **Time Savings.** A site that recently adopted eSource reported productivity gains of 20% compared to their previous paper-based processes, based on more efficient study visits, less printing and managing of paper binders, more efficient quality control processes, and less rework.
- **PI Oversight.** Investigators can review and enter source data at any time, even at satellite locations or when out of the office, providing critical flexibility when reporting and managing a serious adverse event.
- **Quality.** eSource builds quality into the data. It streamlines quality control processes and minimizes the problems to be found and corrected. It helps small sites generate high-quality data without the dedicated quality assurance

personnel and systems of a large site. For sites with multiple locations, it enables remote management and workflow standardization. A third party auditor found that well-designed eSource provides safeguards against half of the most commonly cited protocol deviations.

- **Site Monitoring.** On-site and remote monitors can access study data without study coordinator participation and without exposing the confidential patient information in EHR systems.
- **Resourcing Flexibility.** eSource can guide inexperienced and back-up coordinators through a study visit, and enable sites to speed the process of onboarding new employees.

The Challenge of Complexity

eSource adoption is accelerating as costs come down, the technology is refined, and eSource proves itself in practice. In addition, a major new benefit has emerged: dealing with the increasing complexity of study protocols. This complexity is especially problematic because precision medicine is reducing the number of study participants each site can enroll in a specific study, thereby requiring study coordinators to manage an increasing number of studies, each with its own complicated protocol.

Take, for instance, something as routine as blood pressure measurements. Table 1 presents just a few permutations found in actual protocols:

Table 1. Variations in Blood Pressure Measurements

A	Take blood pressure once after five minutes in sitting position Use same arm throughout study
B	Take blood pressure once after five minutes in sitting position, and a second time, three minutes later Use same arm throughout study
C	Take blood pressure once after 10 minutes in supine position, and a second time, three minutes later in standing position
D	Take blood pressure once after five minutes in sitting position At Visit 1, take blood pressure on the other arm, as well Thereafter, take blood pressure on the higher of the two arms
E	Take blood pressure twice and average them If average > 140 systolic or > 80 diastolic, take blood pressure a third time If third > 140 systolic or > 80 diastolic, subject is ineligible

This complexity extends throughout most studies, from elaborate eligibility criteria, to rating scales, to subject washout rules, to IP administration, to labs, to pre-visit requirements like fasting, etc. Certain types of adaptive trials, especially basket trials, in which the treatment for a specific subject depends on various molecular biomarkers, increase the complexity to an even higher level. Clinical scientists do not create this complexity for amusement — they believe it is necessary to answer a scientific question as efficiently as possible. It thus becomes even more important for sites to follow the protocol exactly.

It is unrealistic to expect even experienced study coordinators to consistently follow such a diverse variety of complex protocols with flawless precision. And, of course, many study coordinators are not experienced, or have to fill in for a primary study coordinator from time

to time. Nor does every study coordinator have the time — or personality — to understand, remember and follow multiple complex protocols to the letter, even assuming that every protocol is written clearly and unambiguously.

Regulatory Compliance

FDA's 2013 guidance, "Electronic Source Data in Clinical Investigations," confirmed that eSource documentation is acceptable to the FDA, provided it complies with 21 CFR Part 11 requirements, such as the existence of an unalterable, user-identified, and timestamped audit trail of all initial and modified data entries.

eSource has substantial data integrity advantages over paper source documents: Paper-based systems allow backdating and data fabrication to "clean up" problems. In contrast, eSource systems timestamp everything and minimize the number of problems that need to be cleaned up.

However, if a site's workflow relies on giving study coordinators the "flexibility" to backdate data entry or for investigators to predate or backdate signatures, adopting eSource would require changing the workflow. A well-designed eSource system should have workflow processes that recognize the fluid, real-world nature of site workflows.

For example, it is common for the investigator to prepare a progress note prior to a study visit, come into the exam room in the middle of the visit to perform a history and physical, sign the progress note at that time, and then fix it if an issue arises later in the visit. With eSource, a better solution is to allow the investigator to create a progress note template prior to the visit, complete a draft version during the visit, and then finalize and "publish" the note after the visit.

The Future of eSource

Widespread adoption of eSource is only a matter of time. Not too far in the future, we will look back on paper source documents like the hand-copied manuscripts of medieval times, but without the beauty or elegance. eSource, eRegulatory binders (ISFs), eConsent, risk-based and remote monitoring, mHealth devices, visual analytics, etc. are all part of an inevitable wave of modernization. The growing complexity of study protocols, unceasing financial pressures, and the rationalization (i.e., consolidation) of a fragmented industry, all demand modernization.

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