August 5, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, R., 1061
Rockville, MD 20852
ATTN: Leslie Kux, Associate Commissioner for Policy

RE: Docket No. FDA-2015-N-1887 – "Source Data Capture From Electronic Health Records: Using Standardized Clinical Research Data"

Dear Ms. Kux:

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics, and medical devices – from discovery, pre-clinical, proof of concept, and first-in-man studies through post-approval and pharmacovigilance research. With more than 110,000 employees engaged in research activities around the world, ACRO advances clinical outsourcing to improve the quality, efficiency, and safety of biomedical research.

Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 research sponsors annually, and we have a broad and unique understanding of the roles, responsibilities, and behavior of all the stakeholders – research sponsors, investigators, Institutional Review Boards, clinical trial participants, and ancillary providers of all types – that are part of the research enterprise.

Representing companies that use Electronic Data Capture (EDC) to collect clinical trial data, ACRO thanks the FDA for soliciting demonstrations and feedback on the use of end-to-end Electronic Health Record (EHR)-to-EDC data sharing, as single-point data capture advances a critical component of the mission of ACRO member companies during clinical trials: ensuring data quality and integrity.

Description of a Viable Standards-Based Option for System Integration

To adequately respond to the Questions for Stakeholders, a plausible model for EHR-EDC integration will be described. ACRO understands that this solution may or may not resemble the future-state integration, if/when it comes to fruition. However, positing a particular structure for EHR-to-EDC integration permits a concrete exploration of benefits, challenges, and gaps between current and future-state workflows.

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There are three goals for the hypothetical integration we envision: 1) to maintain competition in both the EHR and EDC technology spaces; 2) to limit data privacy issues by relying on existing regulations and processes; and 3) to build upon existing data standards such as, but not limited to, HL7 and BRIDG. In this structure, EHR and EDC systems continue to function independently, with a unidirectional data flow from the EHR to the EDC, potentially through a central data repository. EHR vendors would be required to create exports or interfaces, using a set of standard measures for certain biometric data (e.g., height, weight, blood pressure) and coded data (e.g., CPT codes, ICD-9/10 codes, NDC numbers), that could be imported or accepted by any EDC vendor. Adoption by EHR and EDC vendors would be necessary for data transfers to be accomplished, and all vendors would have to complete the build individually for universal data transfer.

End users from one system would not need access to the other, except in instances of data review which would be limited to a subset of users. Patient data would exist in both systems with only pertinent demographic and clinical trial data being solicited by the EDC from the EHR. Clinical trial data gathered in the EDC would not be transferred back into the EHR in order to maintain a distinct difference between the patient's health record and the data gathered during the clinical trial to which the patient consented. This serves the dual benefit of relying on existing structures and policies for access provisioning and security while ensuring that confidential information in the EHR, or any segmented record data, could be kept secure in that system. In contrast, a system structure where EDC users could "peer-in" to the EMR to view and pull data presents a number of challenges, including complicating access provisioning by requiring varied access for diverse clinical entities and necessitating the sequestration of non-research prudent data. Finally, maintaining distinct systems eliminates a need for re-certification of products. For example, any EDC deemed to be 21 CRF Part 11 compliant would still be used and no new system would need to be certified.

What other potential benefits to stakeholders can be achieved through the use of a standards-based technology solution focusing on EHR and EDC integration?

As identified by the FDA, there are numerous potential benefits to standards-based system integration. Improving data quality by electronically collecting source data and eliminating duplicative work, such as transcribing data or filling out study forms, are inherent advantages to using single-point capture of source data. In addition to these, there are nuanced improvements that will improve the process of conducting clinical trials. The integration of EHRs and EDCs would provide benefit both during individual clinical trials, improving immediate and longitudinal patient safety while providing broader analysis of research and clinical care interventions, as well as institutionally, providing increased communication between health care and clinical research organizations.

Paramount in clinical research are the rights and safety of consenting patients. The integration of EHR data into the EDC has the potential to improve patient safety by providing a real-time (or near real-time) analysis of a patient's well-being. Inclusion of biometric data gathered during routine or emergent healthcare visits, the types of visits which are usually inaccessible to researchers as they are not part of the protocol, could help researchers identify health concerns, or even side-effects of, the intervention. Increased access to patient health data during a clinical trial might decrease reliance on post-market

studies to identify negative health impacts by finding correlative adverse events prior to the drug's approval. Also, despite having more data available, collecting source data in the clinical setting and transferring it to the EDC would lower the incidence of fraud or data manipulation. Electronically received values eliminate the possibility of incidental misconduct. And, requests to update data in the EHR in case of noted errors would generate an audit trail. Both of these improvements lead to safer studies.

Clinical studies rely on patient trust and an understanding that there are risks and benefits of the trial for the individual and the systemic development of products. Combined with safer studies as mentioned above, EHR-EDC integration could bolster patient participation by permitting the creation of patient registries based on coded clinical content. Sponsors of open clinical trials that are searching for participants could reference those registries to find available populations and contact Primary Care Physicians or specialists as appropriate. This would also improve healthcare provider's awareness of active clinical trials, encourage conversations between care providers and their patients regarding experimental interventions, and generate excitement for technological advances. Improving patient participation is a key step in accelerating clinical trials, decreasing costs, and developing new, safe, and efficacious cures.

Interoperability in healthcare has a goal of uniting systems to leverage the power of big data in pursuit of new treatments and cures. The integration of EHRs and EDCs is truly the integration of clinical care and clinical research to create a system where patient care begets new innovations which begets improved patient care. A standards-based solution would decrease the need for data queries and data cleaning, slow and expensive processes that instill potential for error. Those administrative costs could be used instead on advanced analytics with a goal of improving health outcomes and lowering costs. Simply, a large, semantic-driven infrastructure would permit broad insights and would support the discovery and development of new products. The benefits gained by this data network, in conjunction with the above mentioned benefits and those in the Notice, provide great utility to healthcare institutions, research groups, and the global population; EHR-EDC integration would allow for a better allocation of funds and man-hours to be dedicated to the pursuit of improving healthcare.

What are the challenges to the implementation of a standards-based technology solution focusing on EHR and EDC integration?

As with any system integration, ACRO has concerns over the costs and time needed to accomplish such a complicated task. With so many EHRs and EDCs in use, it is necessary to consider the measurable savings (e.g., decreases in administrative time, improved monitoring processes) in contrast to the upfront costs of creating hundreds of tailored interfaces. Of particular issue is that most of the savings exist for the organizations using EDCs as the clinical research groups will benefit from the data being input during clinical encounters. However, the costs are more evenly split with both EHR vendors and EDC vendors needing to abide by, and build systems to account for, a standards-based solution. Each challenge below incorporates additional staff, thus time and cost. There is potential for the immediate fiscal benefits to be negated due to project complexity. In this integration, there are nuanced issues. A simple query relating to the receipt of "wrong data" could mean that the patient was wrong, the data sent was incorrect, or it was received in an unreadable format.

The first challenge facing a standards-based technology solution to EHR and EDC integration is patient identification across systems. EHRs and EDCs often use multiple alphanumeric patient identifiers within an organization, and those identifiers could be redundant with identifiers at other organizations even though the identifiers may represent different patients. Patient identification is often done using multiple demographic factors including, but not limited to, name, social security number, and address. These multi-factor identification processes require manual reconciliation when sending or receiving information outside of a system to ensure that information for the proper patient is being transferred. If EHR-EDC integration proceeded with an interface or export/import, patient identification would be crucial to ensure that the protected health information (PHI) would populate the chart of the proper patient. The implementation of a universal system for patient identification would facilitate this process. Creating this unique identifier is a simple task, but there would need to be a process for creating and maintaining these identifiers to ensure that there would not be any duplication. Also, there would be issues of communication when trying to apply the identifier to patients already in healthcare systems. That is to say, a patient with records in multiple healthcare systems could accidentally be given two unique identifiers, which would defeat the purpose.

Once the patient was properly identified, there would be the complex task of properly mapping data so that it could flow from one system into another. This would require both systems to have discrete values for a given measure, which could require development for an EHR or EDC. The potential for shared data is staggering, so it would likely be necessary to have a list of determined sharable data points. This would provide EHRs and EDCs with the knowledge of the data that they would need to be able to send and/or accept. Simple examples would be demographic data (e.g., name, patient identifier, contact information), basic vitals data (e.g., height, weight, blood pressure), medications, and lab data. Without agreement on sharable values, data could be made available by an EHR that was not useful for the EDC. A forum including stakeholders from both systems would likely be necessary to generate consensus on values to share, and processes for adding future values.

With properly identified patients and data elements, there is still the complicated task of ensuring that the data sent can be properly received and understood. As there are various ways to store representations of data, to say nothing of differences in units of measurement, it would be crucial to determine standards for data storage and description. There are some standards for data transfer in the EHR and EDC space, including HL7, CDISC BRIDG, and CDISC SHARE. Successful when followed, these tools could potentially provide a framework for the semantic concerns with transmitting and parsing health data. Following the generic determination of the elements to be shared, a technical project to determine data structure would be necessary, as would a requirement for the EHRs and EDCs to adopt the standards set forth. There would, again, be concern about management of new data elements that could be added in the future. Only at this point, after solving problems about patient identification, data values to send, and semantic structure for incoming and outgoing interfaces could vendors create the required interfaces.

The three issues identified above would need to be solved prior to a go-live and will require the initiative of a central leadership supported by key stakeholders from EHR and EDC vendors and from clinical practice. They aren't, however, the only challenges to the group as a whole. These lengthy projects will require human capital and may limit the input of smaller healthcare and research groups that are not able to provide resources to the project. Once live, the system would need to determine methodology

for data correction. Clinical healthcare data from the EHR is not infallible; a communication method may be necessary to evaluate potential errors noted by users in the EDC, thus preserving the integrity of the source data. Further complicating matters is the increasingly global approach to healthcare and research. That is, EHR-to-EDC system integration could potentially reduce global harmonization. Clinical trials occur globally, and while, longitudinally, there could be a goal of global adoption of these standards, the pursuit of this integration could supersede short-term goals that may provide more benefit. All of these concerns point to this being a resource-intensive project, and one that may not provide the cost and time savings envisioned.

What are the gaps between the data collected in a healthcare setting by EHRs vs clinical research data required for regulated drug development?

The clinical research process requires additional documentation and data collection, specifically related to patient consent, clinical data, and safety data. However, in the integration structure identified above, the EHR supplements the EDC with clinical data, so no additional data or documents would need to be collected within the EHR. For example, informed consent is required for clinical trials. This could still be administered by research staff and collected within the EDC as opposed to being transferred from EHR to EDC. Clinical data, particularly the coded CPT or ICD codes used for inclusion and exclusion criteria, would be transferred from the EHR. Particular diagnoses or pertinent negatives are useful at multiple times in the research process: 1) registries could be built using coded historical patient data; and 2) diagnoses and negatives could be validated to ensure that side-effects are not present.

Safety data and documenting of adverse events is necessary for clinical trials and is not standard practice for clinical care. This could be an integration point as patients may see their Primary Care Physician if they fail to attribute adverse events to the experimental intervention. By providing users in the EDC with data from visits, adverse events that may have previously been missed could be captured. The documentation of the adverse events would still stay within the EDC for submission to the Institutional Review Board (IRB).

Are there any perceived regulatory obstacles to the implementation of a standards-based technology solution focusing on EHR and EDC integration? (Examples include: Source data verification, remote monitoring, 21 CFR part 11, patient privacy, access control, and confidentiality safeguards)

One regulatory obstacle to EHR-EDC integration relates to the patient's right to access his/her own record. This is true within the confines of an EHR where the patient can request a copy of his health record, as well as requesting correction of errors. Contrary to this, a patient in a clinical trial cannot access data collected as part of the trial, which is stored within the EDC. In the EHR-EDC integration method described in this comment, both systems are maintained which eliminates this concern. But, in a shared system approach, clinical trial data would need to be sequestered from clinical data and not be part of the patient's health record.

Source data verification and monitoring, highlighted in the Notice, could both generate regulatory obstacles and are intrinsically linked in clinical trials. Source data needs to be maintained and there is the potential in a clinical setting that values entered into the EHR are transcribed from some other source document. If the EHR data is considered as source data, there would be no way to account for

any of these transcription errors. There is also a regulatory issue regarding the source data following the data transfer. Despite being the same values transmitted via an electronic exchange, the data in the EHR could be considered the source data. In this case, monitors would need to review the EHR to ensure the integrity of the data. There could be access provisioning issues, providing a monitor with EHR access, and it would likely be necessary to truncate the patient's medical record so that the monitor would not have unbridled access to PHI.

Are there any obstacles to the implementation of a standards-based technology solution focusing on EHR and EDC integration?

There are obstacles to implementation relating to proprietary information and cross-industry agreement. There may be concerns that requiring the companies to share data in a certain format infringes upon the competitive advantage or the intellectual property of a given vendor. That is to say, data storage or communications may be a strength of a vendor and forcing universal participation in an integrated EHR-to-EDC system could damage the value of their product as it relates to competitors. The other obstacle is the large-scale coordination between technology vendors and clinical staff necessary to develop and implement standards that will permit the sharing of health data. As clinicians and researchers identify crucial data that should be shared, technology providers will have to develop standard methods for data transfer that can themselves adapt to a rapidly changing technological landscape (e.g., tool used to take blood pressure). This is not an insurmountable task but it may require the guidance of an impartial association which currently doesn't exist. Additionally, these agreements and decisions will likely have a global impact which will need to be considered to ensure the success of future clinical trials.

What standards-based solutions may exist?

Currently, there are three types of standards-based solutions that exist that could facilitate this data transfer. The first are current standards for clinical data transfer (e.g., HL7 and CDISC BRIDG). These are tools that are in place to facilitate faster adoption of new technologies by using standard semantics. While they are not sufficient, they would provide a starting place for this integration process. The new HL7 standards framework, Fast Healthcare Interoperability Resources (FHIR), provides a source of optimism as the modular components are created in such a way as to solve clinical and administrative problems cheaper than alternative solutions. Additionally, FHIR will work across various contexts including EHR-based data sharing, cloud and server communication, and mobile apps. Still, this integration would require a gap-analysis to determine where similar semantic language exists between the standards, but could be useful in identifying subsets of larger data elements that could easily be missed. The second standards-based solution are the current codes for medications (NDC), procedures (CPT), diagnoses (ICD-9 and ICD10), and other medical terms (SNOMED). These codes provide a common language for talking about various aspects of healthcare and are currently in use for EHR and EDC systems, though potentially not always as discrete values. Additionally, Natural Language Processing may be able to help suggest coded values, which could be useful. Finally, Application Programming Interfaces (APIs) could be used to pull patient data. As EHRs continue their progress towards web-based platforms, API requirements could enable researchers to have access to information from previous clinical visits. This solution could work devoid of any interfaces making it a potentially cheaper, less time-intensive process to get some of the desirable data out of EHRs and into EDCs.

Concluding Remarks

The goal of integrating EHRs and EDCs is admirable and would provide for a cycle of patient care, discovery, development, and improved patient care. By incorporating research and clinical trials more closely with clinical care, additional patients will become involved in trials, and trials will become safer and more effective at ascertaining results. The benefits described in this comment and those in the Notice are attainable and will all serve to better the lives of citizens globally.

Please do not hesitate to contact ACRO if we can provide further information. We look forward to the prospect of demonstration projects and hope that the obstacles are not insurmountable.

Respectfully submitted,

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