Biotechnology Innovation Organization

July 18, 2016

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2016-D-1224: Use of Electronic Health Record Data in Clinical Investigations

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance entitled "Use of Health Record Data in Clinical Investigations" (Draft Guidance).

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

GENERAL COMMENTS:

Electronic health record (EHR) data and "real world evidence" generated from the post-marketing clinical use of medicines can provide valuable information regarding the use, benefits, or risks of therapies. BIO applauds FDA for taking steps to provide greater clarity around the use of EHR data in clinical assessments of safety and effectiveness in regulatory submissions.

In general, the Draft Guidance is helpful and well-constructed, providing useful information to assist sponsors in incorporating and integrating EHR data into FDA-regulated clinical investigations.

As the Draft Guidance notes, EHR systems are generally not under the control of FDA-regulated parties, which presents numerous operational challenges as FDA seeks to assess and ensure the validity, reliability, and integrity of data originally generated by non-FDA regulated parties. To that end, BIO requests additional clarification regarding the responsibilities of the sponsor and how the Agency intends to uphold EHR data standards through on-site inspections and audits. Additionally, the draft guidance should acknowledge the EHR responsibilities of the PI (and of the associated organization/institution) making clear distinctions between the Sponsor and PI.

Similarly, it would be very helpful to have additional clarity related to a sponsor's responsibilities regarding extracted data; for example, what checks might be necessary when data is transferred to the sponsor's system, and whether sponsors could extract data

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ready for analysis on a server without entering it into a structured database (such as an electronic data capture (EDC) system).

As indicated in the below chart, there are a number of other topics on which further detail would be helpful, such as the assessment of ex-US electronic health record data, as well as practical implementation of some of the recommendations in the Draft Guidance.

In addition, we suggest that FDA provide additional guidance related to the use of clinical notes; as well as confidentiality, use, and interpretation of non-structured data in clinical investigations. Sponsors would also benefit from clarification regarding the Agency's position on de-identified data, and how it affects any applicable privacy requirements.

Lastly, we recommend that FDA consider an initiative to better align data standards between EHRs and clinical trial submissions. EHRs are encouraged to follow applicable Health Level 7 (HL7) standards, yet clinical trial submissions generally adhere to Clinical Data Interchange Standards Consortium (CDISC) standards. Greater alignment between these sets of standards would foster greater consistency and facilitate interoperability.

BIO appreciates the opportunity to provide comments to the Draft Guidance entitled "Use of Electronic Health Record Data in Clinical Investigations." We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely

/S/

Scott V. McGoohan, J.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

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I. INTRODUCTION		
II. SCOPE		
Lines 64-69:	The Draft Guidance states that, "The recommendations outlined in this guidance apply to the use of EHR data in prospective clinical investigations of human drugs and biological products, medical devices, and combination products. This includes foreign clinical studies not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE) that are submitted to FDA in support of an application for the marketing approval of a medical product (see 21 CFR 314.106, 312.120 and 814.15)."	BIO asks the Agency to provide further details on how the integrity of the data in studies conducted outside the US can be assessed or assured. Not all trials will undergo audit, nor at the same time points. The Agency may need to specify different parameters or requirements for data integrity in foreign studies for the 3 periods when audits may occur: prior to trial initiation, during the study, and after completion.
Lines 71-77:	The Draft Guidance states that, "This guidance does not apply to the use of EHR data: • In postmarketing observational pharmacoepidemiologic studies designed to assess the risk associated with a drug exposure or designed to test prespecified hypotheses for such studies • When used as a recruitment tool for clinical investigations" The Draft Guidance does not require the use of EHR as source data in studies. It does, however, provide recommendations for "deciding whether and how to use EHRs as a source of data" (line 29) and "using EHRs that are interoperable" (line 31) with traditional	BIO recommends that FDA consider not excluding postmarketing pharmacoepidemiology studies from the scope of the guidance, and instead modify the language as follows: "This guidance does not apply to the use of EHR data: ~~• In postmarketing observational pharmacoepidemiologic studies designed to assess the risk associated with a drug exposure or designed to test prespecified hypotheses for such studies~~ • When used as a recruitment tool for clinical investigations" Additionally, BIO asks that the Agency please clarify if the guidance applies to randomized controlled Phase 4 trials not

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	electronic data capture systems. There are indeed potential numerous benefits to using EHRs as a source of data (lines 98-108): data accuracy, study efficiency, post-study follow-up for long-term safety and efficacy, long-term follow-up of large numbers of patients on rare endpoints. However, the same benefits would also apply to prospective observational cohort studies (prospective registries or observational trials). In fact, the Draft Guidance focuses on improving requirements for EHRs as a real world data (RWD) source (e.g., EHR as the focal point for integrating multiple data sources). The rationale for excluding prospective observational studies from benefitting from the same enhancements to EHRs is unclear. Real world evidence (RWE) derived from innovations in RWD sources like EHRs is increasingly being recognized by both FDA and payers as an essential part of the total evidence package in understanding the complete benefit/risk picture. The quality of RWE will also be improved by ensuring the consistent availability of more reliable and richer data from EHRs. Finally, we agree the use of EHR data to aid recruiting for clinical trials does not require the same level of quality control. However, the greater standardization, quality and richness of EHR data resulting from this and other guidance documents	intended to support new claims of efficacy or safety (or "label expansion"). For example, Phase IV observational trials or investigator initiated trials. As currently written, it is unclear whether these studies are included under the scope of the guidance.

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	should also greatly increase its utility for patient recruitment in trials and for optimizing protocol design. In the era of precision medicine, the ability to more accurately identify and recruit patients based on matching of eligibility criteria using the increasingly rich data becoming available from EHRs (clinical, lab, imaging and genomic) could greatly benefit patients by speeding access to trials, and reduce the time and cost of studies for sponsors.	
III. BACKGROUND		
Lines 88-90; 168-170; and 176-178	The Draft guidance states that, "In general, EHRs are not under the control of FDA-regulated entities (e.g., sponsors, clinical investigators), because in most instances, these systems belong to health care organizations and institutions." However, the rest of the guidance places obligations on these entities, primarily sponsors, that have the effect of suggesting that sponsors should exert control over these systems. For example, Lines 168-170 instruct the sponsor to "ensure that the appropriate authority controls and in place to limit system access." Lines 176-178 state that "sponsors should ensure the EHRs they use and the processes and policies for their use provide electronic source data that are… (ALCOA). Since clinical trial sponsors do not generally use EHRs of their own, this statement presumably places the burden on sponsors to assess/audit institutional/HCO EHR. Each sponsor may require changes to related these systems and/or	

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	institutional policies and procedures to meet FDA's "ALCOA" standard (which is not defined in regulations and therefore is subject to differing interpretations). The net impact is that a single health care organization used by multiple sponsors may face ongoing and conflicting requirements from sponsors related to policy documentation, system documentation et al. This does not "encourage the use" of EHR as a source of clinical trial data; rather, it discourages it and may slow the activation of sites, the conduct of trials, and the generation of evidence needed by clinicians, patients, and consumers to make decisions about the use of medical products.	
Lines 104-107:	The Draft Guidance states that, "EHRs may have the potential to provide clinical investigators and study personnel access to real-time and longitudinal health care data for review and can facilitate post-trial follow-up on patients to assess long-term safety and efficacy of medical products."	BIO requests clarification as to how a sponsor can ensure that the required or valid adverse event data (e.g., SUSARs) are captured from EHR into the EDC system? Will that require a manual step to identify and capture the "unexpected"? Or does it mean that all AEs will be captured in the EDC system - which is not what the current FDA standard mandates.
IV. INTEROPERABILITY		
Lines 111-170:	Section IV does not explicitly address HER data pulled into a cloud, for aggregation or otherwise (*e.g.*, pooling multiple EHRs from multiple hospitals), and then EDC from this cloud, rather than direct from HER. BIO seeks clarification regarding whether such practice would be allowed, or excluded as the Draft Guidance discusses direct EHR to EDC.	BIO suggests clarifying that the recommendations contained in the Draft Guidance apply to various EDC systems, including those pulled from cloud-based systems.

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Lines 136-138:	The Draft Guidance states that, "Interoperable technology may also allow full integration of the EDC system with the EHR so that the clinical investigator and the patient's other health care providers would have access to all of the research and clinical care data as appropriate."	BIO requests clarification of the regarding use of the phrase, "*access to all of the … data as appropriate*." Is it really "all" data or just the "appropriate" data? Who decides which and how is this determined: by the "system" or interoperable EHR data standards in general, or individually by the investigator on each trial? The potential uses and clinical and research impact of accessing this data is unclear, particularly as it relates to trial integrity.
Lines 141-143:	The Draft Guidance states that, "In addition, an interoperable EHR-EDC system could provide the ability to integrate with other health care clinical information systems (e.g., radiology information systems, laboratory information systems)."	EHR systems may already incorporate the health care information contained in radiology information systems and laboratory systems. The EHR is a transactional system to capture data about individual patients and support physician decision-making about individual patients. EHRs are generally not designed for, nor necessarily the best or appropriate system as a source of data for research. BIO recommends that FDA consider that EHR and/or the Research Data Warehouse could be allowed as the source of data for use in clinical investigations.
Lines 148-155:	The Draft Guidance states that, "There can be many practical challenges to the interoperability of EHRs and EDC systems. These challenges may include the complex and diverse clinical data standards used by the health care and clinical research communities, which may hinder the exchange of information between different electronic systems. Also, diverse ownership of electronic systems and data can necessitate appropriate collaboration between the health care and clinical research communities. Many	While the Draft Guidance does include comments related to challenges with data standards, BIO encourages the FDA to provide more specific guidance on harmonization for various existing and emerging uses of EHR data. There are significant ongoing efforts to use EHR data for health system/clinical performance improvement, quality measurement and reporting and research. There may be a risk of multiple divergent efforts to reuse EHR for different

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	of these challenges are being addressed by the adoption of data standards as well as through standardization requirements as part of the ONC Health Information Technology (Health IT) Certification Program."	purposes. FDA's guidance will be helpful in pushing the industry towards increased collection of data in routine clinical care that may serve multiple purposes. For example, FDA could build upon the work of the ONC and recommend principles that support interoperability and encourage more efficient collection and use of data.
Lines 158-161:	The Draft Guidance states that, "However, if the data elements obtained for the sole purpose of a clinical investigation are entered directly into the EHR by study personnel (e.g., by using a dedicated research module within the EHR), the individual entering the study-specific data should be identified as the originator." How activities carried out for the "sole purpose" of research will be distinguished is not clear; a dedicated research module could captured activities that are carried out both for the trial and for the purposes of clinical care of the patient. In practice, this recommendation may be a challenge to implement and may be interpreted in different ways during FDA inspections.	BIO questions whether this recommendation is feasible in practice, and recommends deleting the sentence: ~~"However, if the data elements obtained for the sole purpose of a clinical investigation are entered directly into the EHR by study personnel (e.g., by using a dedicated research module within the EHR), the individual entering the study-specific data should be identified as the originator."~~
Lines 168-170:	The Draft Guidance states that, "In such cases, the sponsor should ensure that the appropriate authority controls are in place to limit system access for entering and modifying data to the research component of the EHR to study personnel only."	This section implies that there will be a special research section of EHR for non-routine data. We ask the Agency to clarify whether this will be a separate system or module or whether this could be included within the current EHR workflow, for example, an extra box on a data collection

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		screen. EHR designers should be encouraged to implement such a dedicated research module as both a control to ensure that only the necessary patient identifiers are transferred to the EDC and also, at the Institution's option, to allow for remote monitoring of source documents in a way that ensures both security and privacy. Academic and research-oriented healthcare delivery organizations may already have dedicated systems for EDC of research data (*e.g.*, such as REDCap or Velos). Smaller community healthcare organizations may rely on the vendor marketplace for system support. FDA should consider the potential impact of their guidance and incentives on subsequent system development and architectures. For example, will the guidance encourage proliferation of a multiplicity of diverse EHR research modules of varying quality by different EHR vendors, as opposed to a few best-practice research EDC systems and/or data warehouses?
V. BEST PRACTICES FOR THE USE OF EHR DATA IN CLINICAL INVESTIGATIONS		
A. Use of ONC-Certified Health Information Technology		
Lines 183-186:	The Draft Guidance states that, "The Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH Act) requires that ONC establish a voluntary certification program for health IT. ONC has adopted use of the broader term health IT in the ONC Health IT Certification Program that includes EHRs and other forms of health information technology that provides electronic data."	BIO recommends that FDA add a link to accredited organizations providing certifications (*see:* https://www.healthit.gov/sites/default/files/pdf/fact-sheets/ehr-certification-program.pdf). This may be helpful to provide context for this paragraph and may be helpful for those not familiar with an ONC Health IT Certification Program.

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B. Use of EHRs Not Certified by ONC		
Lines 201-203:	The Draft Guidance states that, "Specifically, for EHRs not certified by ONC, sponsors should consider whether such systems have adequate controls in place to ensure that the confidentiality, integrity, and reliability of data are preserved."	BIO requests clarification regarding the definition of "adequate controls," and the inclusion of examples of how such controls can be "put in place to ensure that the confidentiality, integrity, and reliability of data are preserved." Also, BIO notes that ONC is a standard primarily used in US-based data. BIO asks that FDA clarify whether more globally accepted standards such as GXP would also be acceptable.
VI. OTHER GENERAL CONSIDERATIONS FOR BEST PRACTICES		
A. Use of EHRs in Clinical Investigation		
Lines 233-236:	The Draft Guidance states that, "Therefore, sponsors should include (e.g., in the protocol or the data management plan) information about the intended use of the EHR during a clinical investigation and a description or diagram of the electronic data flow between the EHR and the sponsor's electronic system supporting the clinical investigation." The above language suggests that a single EHR ("intended use of the HER" [underlining added]) will be used that can be concisely described or diagramed in the protocol or data management plan. However, a sponsor conducting a global trial may be potentially integrating data from multiple EHR systems from different vendors.	BIO requests that the Agency clarify expectations regarding documentation (*e.g.*, the level and amount of detail required), and whether documentation can be general, or does FDA expect documentation of how each different EHR system will be utilized. If the latter, will the protocol or data management plan require amendment each time a new site using a different EHR vendor or version is added? Additionally, for multi-site investigations, the EHR at each specific site may be different, requiring site specific descriptions of use. Is the intention to recommend all site specific data flows are documented or to describe the overall EHR, high level description?

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Lines 236-242:	The Draft Guidance states that, "This should include a description of how the relevant EHR data are extracted and subsequently imported into the sponsor's electronic system. Sponsors should check the extracted data for consistency and completeness with the source data obtained from the EHR, and make corrections when errors are found to properly align the source data with the extracted data. In addition, sponsors should ensure that data obtained from the EHRs are consistent with the data collection specified in the clinical protocol." The Draft Guidance may unintentionally undermine FDA's 2013 Guidance on risk-based monitoring and the draft addendum to the ICH E6 guideline to which FDA is a party through requiring sponsors to "check the extracted data for consistency and completeness with the source data from the EHR and make corrections when errors are found to properly align the source data with the extracted data. The Draft Guidance suggests that any error, no matter how trivial, should be identified and corrected and is missing the Agency focus on "critical data" found in other guidance and Agency publications (e.g., Enhancing clinical evidence by proactively building quality into clinical trials. *Clinical Trials*. Published online before print April 20, 2016, doi: 10.1177/1740774516643491).	BIO recommends that the FDA amend the Draft Guidance to be in line with the Agency's 2013 Guidance on Risk-Based Monitoring and the Agency's focus on "critical data." Additionally, BIO requests clarification as to the purpose of the error checking process. Is it intended as a quality check (e.g., record counts, etc.) rather than a manual step for error checking? If not, it seems to undermine the overall purpose and benefit of electronic data transfer. In Risk Based Monitoring (RBM), the model does not mandate 100% Source Data Verification and only part of source data is verified at site. BIO requests that FDA be more precise on expectation on level of check required? Do General RBM rules apply? Lastly, BIO asks that FDA please reference a standard or regulation that specifies the data consistency that sponsors are responsible for.
Lines 244-245	The Draft Guidance states that, "Sponsors should ensure that software updates to the sponsor's electronic system or the EHR do not affect the	BIO requests that the FDA clarify how long this responsibility endures, after last patient out? Inspections can follow years after last patient out; are sponsors required to continue to

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	reliability and the integrity of EHR data entering the sponsor's electronic system."	monitor the HER for software upgrades in such instances? BIO requests FDA clarify how it will handle these types of issues in inspections.
Lines 248-250:	The Draft Guidance states that, "Sponsors should also ensure that study monitors have suitable access to all relevant subject information pertaining to a clinical investigation as appropriate."	BIO notes that access will be managed by an investigational site as EHR is a site-owned system, and requests that FDA provide details on expectations on access control requirements for site monitors.
B. Data Modifications		
Lines 257-261:	The Draft Guidance states that, "When health care professionals who are not part of the clinical investigation make modifications or corrections to data in the EHR that will be used for the clinical investigation, it is important to ensure that these modifications are made without obscuring previous entries. The sponsor's electronic system should capture any updated information as well as any accompanying audit trail information." BIO note that this may be challenging to implement from a system point of view. In which system(s) does this functionality reside? It will be important to specify more clearly the requirements for electronic transfer of data changes and audit trail information.	BIO request that FDA provide additional clarification by specifying more clearly the requirements for electronic transfer of data changes and audit trail information, and providing examples.
C. Audit Trails		
Lines 265-267:	The Draft Guidance states that, "For EHR data gathered during the course of a clinical investigation, sponsors and clinical investigators should ensure that there are adequate methods to monitor, track, and	BIO recommends modifying the text as follows: "For EHR data gathered during the course of a clinical investigation, sponsors and clinical investigators should

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	document all changes made to information in the EHR pertaining to the conduct of the clinical investigation." BIO notes that the availability of the EHR audit trail, associated access, and notification of software updates may need provisions (*e.g.*, escrow arrangement) in contracts to mitigate site ownership or system changes that may occur during a study conduct or archiving period.	ensure that there are adequate methods and provisions (e.g., contractual) to monitor, track, and document all changes made to information in the EHR pertaining to the conduct of the clinical investigation."
Lines 268-270:	The Draft Guidance states that, "Identification of the data originator (i.e., EHR or study personnel entering or modifying the clinical study data) and the date and time data were entered into the EHR should be available to FDA at the time of inspection (see section IV of this guidance)."	BIO requests that the Agency clarify what are the sponsor's responsibilities when they are receiving de-identified or anonymous data.
D. Informed Consent		
E. Privacy and Security of Data		
VII. INSPECTION, RECORDKEEPING, AND RECORD RETENTON REQUIREMENTS		
Lines 305-310:	The Draft Guidance states that, ""Likewise, when the EHR is identified as the source, all relevant data within the EHR pertaining to the clinical investigation must be made available to FDA for review upon request (see 21 CFR 312.62(b), 312.68, 812.140(a), and 812.145). During an inspection, FDA may also request other paper or electronic records to support data in the eCRF (e.g., case histories, other data pertaining to the clinical investigation) (see 21 CFR 312.57, 312.58, 312.62(b), 312.68, 812.140(a)(3),	BIO requests that FDA clarify whether institutions are expected to allow inspectors direct access to EHRs during an inspection.

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	and 812.145).”	