July 18, 2016

The Honorable Dr. Robert Califf
Commissioner
Food & Drug Administration
Attention: FDA-2016-D-1224
Submitted electronically at http://www.regulations.gov

RE: "Use of Electronic Health Record Data in Clinical Investigations; Draft Guidance for Industry; Availability"

Dear Commissioner Califf:

The American Medical Informatics Association (AMIA) appreciates the opportunity to provide input on the Noticed of Availability regarding the Draft Guidance for Industry on Use of Electronic Health Record Data in Clinical Investigations. This Notice was published by the Food & Drug Administration (FDA) in the May 17, 2016 issue of the *Federal Register*.

AMIA is the professional home for more than 5,000 informatics professionals, representing front-line clinicians, researchers, educators and public health experts who bring meaning to data, manage information and generate new knowledge across the health and healthcare enterprise. As the voice of the nation's biomedical and health informatics professionals, AMIA plays a leading role in advancing health and wellness by moving basic research findings from bench to bedside, and evaluating interventions, innovations and public policy across settings and patient populations.

With more than 96 percent of US hospitals[1] and 83 percent of US office-based physicians[2] using EHRs to deliver clinical care, we have an unprecedented opportunity to utilize digitized healthcare data for supplemental uses, such as clinical investigations, especially for prospective controlled clinical trials. Given this view, AMIA fully supports FDA's willingness to consider EHR data as a potential source for FDA-regulated clinical research. We believe this guidance is well-timed and can serve as a valuable signal to industry, and other stakeholders, on how to orient technical functionalities and organizational policies to capitalize on this opportunity. As a picture of the future state, this guidance provides an important window into how interoperable EHRs and electronic data capture systems or electronic case reporting forms could be leveraged to simplify data collection, reduce errors and provide healthcare professionals new opportunity to treat emerging issues that arise as part of investigations. However, we strongly caution FDA from assuming that most EHRs are readily configurable for clinical investigations, even among more advanced institutions.

---

[1] Henry, J., Pylypchulk, Y., et al. Office of the National Coordinator for Health IT, "Adoption of Electronic Health Record Systems among U.S. Non-Federal Acute Care Hospitals: 2008-2015," Data Brief No. 35, May 2016
[2] Heisey-Grove, D., Vaishali, P. Office of the National Coordinator for Health IT, "Any, Certified, and Basic: Quantifying Physician EHR Adoption through 2014," ONC Data Brief, No. 28, Sept. 2015

July 18, 2016

AMIA believes this guidance highlights a number of complex issues, which must be addressed before it can be used as a practical document meant to ensure the quality and integrity of EHR data used in clinical investigations. Specifically, we perceive an overreliance on the assurances resulting from ONC's Health IT Certification Program related to data reliability and interoperability. Further, we discuss ways FDA could improve the likelihood of data integrity when using EHR source data and we raise a number of additional issues for FDA to consider when finalizing this guidance.

We see this guidance serving as an important catalyst for improved dialogue among clinicians, academia, pharmaceutical companies, device makers, and developers of health IT to help inform FDA's understanding of the current state, and to hasten the desired future state. Our feedback, included as an attachment below, highlights where some of this dialogue should occur in the near-term.

AMIA stands ready to help broker such conversations and we look forward to constructive work towards our shared vision of a learning health system and evidence generating medicine. Should you have questions about these comments or require additional information, please contact Jeffery Smith, Vice President of Public Policy at jsmith@amia.org or (301) 657-1291. We look forward to continued partnership and dialogue.

Sincerely,

Douglas B. Fridsma, MD, PhD, FACP, FACMI
President and CEO
AMIA

Thomas H. Payne, MD, FACP, FACMI
AMIA Board Chair
Medical Director, IT Services, UW Medicine
University of Washington

Enclosed: AMIA Response to Draft Guidance for Industry on the Electronic Health Record Data in Clinical Investigations

American Medical Informatics Association | AMIA
4720 Montgomery Lane, Suite 500 | Bethesda, Maryland 20814

July 18, 2016

EHR Data Provenance and Integrity

As we understand it, the primary purpose of this guidance is to help sponsors and investigators understand FDA current thinking when the EHR is identified as the originator of data elements "obtained for clinical investigation in the course of routine clinical care" (157-158). AMIA fully supports FDA's willingness to consider EHR data as a potential source for FDA-regulated clinical research.

However, we note that data collected and used in EHRs are intended to support the care of individual patients, rather than providing research quality data, and often is not of the ALCOA standard (177-178). For example, blood pressure (BPs) recordings in the context of RCTs usually have a strict protocol for how values should be taken, time between checks, position of the patient, cuff type, etc. In EHRs, most BPs are recorded in the same field no matter how, when, where or by whom they were recorded. This lack of standardization will be a tremendous challenge for high-quality, rigorous research. Further, ensuring data integrity and tracking data provenance in clinical settings is incredibly complicated because multiple, authorized individuals contribute to the EHR and the specificity of audit logs varies widely. If FDA is interested in which data populated the EDC system or eCRF and where they originated along the continuum of care, the answer could prove extremely difficult and burdensome.

AMIA Recommendation: We encourage FDA to suggest sponsors look towards enterprise data warehouses or translational data warehouses, especially those that utilize a common data model, such as OHDSI, i2b2 SHRINE, or mini-Sentinel, amongst others. These sources may have better semantic interoperability and data integrity compared to sources that remain in the EHR default data model. At a minimum, FDA should describe which version of EHR data would be considered source (e.g. transactional database, clinical data warehouse, etc.) and what specific criteria are relevant to the determination of 'acceptable' data integrity and provenance.

The Role of ONC's Health IT Certification Program

Sections IV and V mention ONC's Certification Program in relation to interoperability (113-155) and they note how certified EHRs "meet certain privacy and security protection requirements for an individual's health information" (192-193). Further, guidance suggests certified EHR technology gives "FDA confidence during inspections that the EHR data is reliable…" (194-195).

ONC's Health IT Certification Program is not designed to ensure data "reliability" or integrity. Indeed, such integrity and reliability is generally the result of the policies, procedures and actions of the EHR users rather than the technology itself, and we see this guidance overstating the ability of certification to deliver clinical investigation-quality data as a byproduct of care delivery. Further, our members note a general lack of consensus on IT standards used by private sector actors to render clinical data useful for research, which adds to the variability of data quality and potential approaches meant to mitigate data integrity deficiencies.

American Medical Informatics Association | AMIA
4720 Montgomery Lane, Suite 500 | Bethesda, Maryland 20814

July 18, 2016

AMIA Recommendation: We encourage FDA to work closely with ONC counterparts to better understand how current and future certification criteria may enable more reliability through accurate and complete exchange of clinical data for research, including ways to improve / develop technical standards at the boundaries of clinical care and research.

Compliance Confusion & Areas for Future Guidance

As the distinctions between clinical data for purposes of care and purposes of research blur, we foresee a number of compliance and policy issues that will require reconciliation. Below we highlight issues raised in this guidance that may warrant future attention by federal officials.

Data Modifications. Section V.B. (Lines 257-26) may require additional discussion with experts and stakeholders. Most EHRs do not capture data history (original/updated values). Thus, requiring all modifications to data in the EHR be made without obscuring the original data is not practicable. The EHR is part of a dynamic healthcare ecosystem, so while infrequent, there could be changes to data in the EHR after a sponsor pulls it for research, and the sponsor would never know data had changed. FDA's guidance could work if the EHR data *at a given point in time* was considered the source, rather than EHR data as it might exist *throughout time*. Were this the case, FDA could inspect EHR data set extracts as the source data, and compare these against data in the sponsor's EDC system.

Audit Trails. Section V.C. (263-273) discusses "Audit Trails" suggesting that there should be "adequate methods to monitor, track, and document all changes made to information in the EHR pertaining to the conduct of the clinical investigation." While we agree this would be an important capability to preserve reproducibility and detect any tampering, we question the capacity of current EHRs to deliver on these kinds of audit logs.

Use of genomic data. We also foresee a time where genomic data are stored in EHRs as unstructured data that may have relevance to FDA. Genomic data may represent or be used to demonstrate epigenetic or gene-environment interactions with trial drugs that are under review by regulators. FDA should consider this and related use cases and address potential compliance issues, especially as we move into the precision medicine era.

The round-tripping of clinical investigations results back into the EHR. Lines 123-125 say that interoperability between EHRs and EDCs present an "opportunity for health care professionals who are not part of the clinical investigation to be aware of and treat emerging health care issues that arise as a part of the clinical investigation and document such issues in the EHR." While we share in this vision, there are numerous ethical, technical and governance issues surrounding this use case. Future coordination and guidance will be needed.

21 CFR 11 Compliance. We acknowledge FDA will assess compliance with 21 CFR 11 on data derived from the EHR "at the point when that data enter the sponsor's electronic system supporting the clinical investigation" (161-165). We are concerned that the practical impact of this statement

American Medical Informatics Association | AMIA
4720 Montgomery Lane, Suite 500 | Bethesda, Maryland 20814

will move 21 CFR 11 compliance "upstream" to EHR system users and / or developers, by way of sponsor requirements.

Other uses of EHR data. Although FDA excludes observational pharmacoepidemiological studies from this guidance, we encourage additional focus from FDA on these kinds of investigations. Given our concerns around the use of EHR data for RCTs, noted above, we are less concerned about the state of readiness of EHRs for observational studies. This kind of focus may provide an essential developmental stage for FDA to garner experience and accelerate the learning necessary to achieve its goals for clinical investigations. We note there are a number of research consortiums and collaborations that already leverage EHR data in such ways, and we encourage FDA to dialogue with such groups.

American Medical Informatics Association | AMIA
4720 Montgomery Lane, Suite 500 | Bethesda, Maryland 20814