November 29, 2021

Dr. Janet Woodcock
Acting Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Comments submitted via www.regulations.gov

Dr. Woodcock:

The American Medical Informatics Association (AMIA) appreciates the opportunity to provide input on the Real-World Data (RWD): Assessing Electronic Health Records (EHR) and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products Draft Guidance.

AMIA is the professional home for more than 5,500 informatics professionals, representing frontline clinicians, researchers 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.

We applaud the scientific rigor and thoughtfulness with which FDA has approached this guidance. As informatics professionals, we believe in the promise of the Learning Health System to improve health and health care. We view this guidance as an opportunity for the FDA to acknowledge and support the importance of EHR data to the Learning Health System, while also helping researchers expand their constructs of research and the EHR as an important resource to support and maintain this system.

As FDA refines this guidance, we advise it to separately evaluate data from the EHR and those from claims. EHR data is collected as a byproduct of the health care encounter, with data generated by providers, patients themselves, and digital health technologies. Claims data, on the other hand, is a data source generated as a result of an evaluation by a health care professional from the patient encounter. By grouping the two data types, the guidance – perhaps inadvertently – suggests that they are of equal status in the delivery ecosystem, when they in fact have different values and limitations, among other differences.

Finally, we believe that several areas of this guidance would benefit from clearer direction from the FDA. We observe that as written, this guidance underestimates the issue of varying data quality in

RWD, as well as the associated information quality in data generation. The majority of the RWD data sources cannot meet the specifications laid out in this guidance for various reasons. Below we offer specific recommendations for improving this guidance, which we believe will better encourage the industry to leverage RWD for regulatory decision making.

We hope our comments are helpful as you continue this vital work. Should you have any questions or require additional information, please contact Scott Weinberg at scott@amia.org or 240-479-2134. We thank FDA for the opportunity to comment on this guidance and look forward to continued dialogue.

Sincerely,

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Enclosed: Detailed comments on the Real-World Data (RWD): Assessing Electronic Health Records (EHR) and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products Draft Guidance.

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General Considerations

FDA writes that for all studies using EHRs or medical claims data that will be submitted to support a regulatory decision, sponsors should submit protocols and statistical analysis plans before conducting the study. We recommend that FDA provide some guidance on what aspects of the data should be included and will be expected as part of the protocol submission. An FDA-approved Use of EHR and/or Medical Claims pre-study data evaluation process should further be supported using digital technology to provide structure, ease of submission, and timely decisions from the FDA to not delay the conduct of research.

FDA further writes that the use of certain study design features or specific analyses to address misclassified or missing information, as well as methods to achieve covariate balance, will be discussed in other FDA RWE guidance focused on study design and analysis. There are currently many comprehensive methods available to assess data quality dimensions.[1] Because many dimensions, including accuracy and completeness, are quantifiable, future guidance from FDA should address thresholds of data reliability and relevance that will be deemed acceptable by the FDA.

Finally, we recommend that FDA more explicitly underscore the importance of representativeness of RWD in the guidance's discussion on determining data reliability and relevance. An unrepresentative dataset will invariably lead to unrepresentative results and will be a potential source of bias, leading to limitations of any RWE that can be drawn from those data. We therefore urge FDA to better define "representative patients" in its proposed definition of "relevance."

Data Sources

FDA writes about the potential limitations of the relevant data sources, including claims data. With this in mind, we recommend FDA provide additional guidance on what types of studies are appropriate and fit for the use of claims data in the context of regulatory decision-making. In addition, the limits of claims data due to agreed-upon terminologies are problematic. We encourage FDA to work with other relevant federal agencies, such as the National Library of Medicine to develop standard claims data terminologies relevant for regulatory decision making.[2]

FDA additionally claims that a limited ability to add modules to collect extensive additional information during routine, EHR-based data collection may still not be comprehensive. However, we note recent research showing that a pragmatic clinical trial study did not markedly alter the EHR to collect data for research purposes.[3] The value of research outside of the clinical trial is that studies

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[1] Bian, J., Lyu, T., Loiacono, A., Viramontes, T.M., Lipori, G.P., Guo, Y., Wu, Y., Prosperi, M.C., George, T.J., Harle, C.A., Shenkman, E.A., & Hogan, W.R. (2020). Assessing the practice of data quality evaluation in a national clinical data research network through a systematic scoping review in the era of real-world data. *Journal of the American Medical Informatics Association : JAMIA, 27*, 1999 - 2010.

[2] https://www.healthaffairs.org/do/10.1377/hblog20210929.605951/full/

[3] Leather DA, Jones R, Woodcock A, Vestbo J, Jacques L, Thomas M. Real-World Data and Randomised Controlled Trials: The Salford Lung Study. Adv Ther. 2020 Mar;37(3):977-997. doi: 10.1007/s12325-019-01192-1. Epub 2020 Jan 11. PMID: 31927698; PMCID: PMC7147238.

in the real world have access to real world data that is generated from care delivery. While EHR system design can certainly improve, the FDA can provide better guidance into the operationalization of EHRs for clinical purposes without requiring add-on modules and subsequently increase the data collection burden for clinical EHR users.

Relevance of the Data Source

FDA notes that there are differences in the practice of medicine around the world and between health care systems that may affect the relevance of the data source to the study question. We recommend that FDA include additional guidance that directs attention to data on outcomes of care and interventions across the various health care system factors and insurance programs. Guidance about data on confounders is as equally important as data on outcomes that can be linked to these confounders.[4]

As to FDA's recommendations for documenting data relevance, we recommend that FDA, along with relevant stakeholders, provide guidelines on how to identify biases in data and analyze these potential biases. While a demographic breakdown of the included study population (i.e., after applying all inclusion/exclusion criteria) will presumably be required, because of potential biases in algorithms, knowing additional details about the overall data source is valuable. For example, a recent preprint of a systematic review of heart failure phenotyping algorithms shows that while epidemiologically, heart failure affects more women, nearly all published phenotypes for heart failure identify majority male populations.[5] It is not always clear whether this is due to a biased data source (e.g., the VA will almost always be male-skewed) or biased phenotyping algorithms. As RWE becomes routine, this is a critical area to monitor to ensure the representativeness and equity of these findings.

Finally, FDA recommends including a description of prescribing and use practices in the health care system (if available), including for approved indications, formulations, and doses. If these data elements are indeed important for evaluating RWE for regulatory decision making, then FDA should coordinate with standards setting agencies within the federal government to develop standards for these important data elements. FDA should seek to align its standards with the USCDI within and leverage data standards for USCDI v2 Provenance (Author Organization) and USCDI Level 2 Medications in order to ensure consistent use of data for these recommended data elements. FDA should further provide background as to why these data sources are essential for regulatory decisions using RWE.

Data Capture: General Discussion

FDA writes that continuity of coverage should be addressed when using EHR and medical claims data sources, given that patients often enroll and disenroll in different health plans when they

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[4] Veet, C.A., Radomski, T.R., D'Avella, C. *et al.* Impact of Healthcare Delivery System Type on Clinical, Utilization, and Cost Outcomes of Patient-Centered Medical Homes: a Systematic Review. *J GEN INTERN MED* **35,** 1276–1284 (2020). https://doi.org/10.1007/s11606-019-05594-3

[5] Rebecca T. Levinson, Jennifer R. Malinowski, Suzette J. Bielinski, Luke V. Rasmussen, Quinn S. Wells, Veronique L. Roger, Laura K. Wiley. medRxiv 2021.02.01.21250933; doi: https://doi.org/10.1101/2021.02.01.21250933

experience changes in employment or other life circumstances. We believe that more guidance is needed on the definitions of continuity of coverage vs. continuity of care within a health care delivery system. A patient may move from payer to payer, however stay within the same health care delivery system. It is possible that a patient may change payer and change care delivery site, however because EHRs can potentially be linked across different delivery systems, the continuity of care data for a patient is still possible. FDA should provide clear guidance that distinguishes the two scenarios, as well as guidance on how it expects to see analysis on data from multiple EHR systems.

FDA additionally writes that in general, EHR and medical claims data do not systematically capture the use of nonprescription drugs or drugs that are not reimbursed under health plans, or immunizations offered in the workplace. If these exposures are particularly relevant to the study question, the protocol should describe how this information will be collected and from what source, given that EHRs and medical claims data are insufficient. FDA should provide further guidance on how acceptable these new sources of data (nonprescription drugs or drugs that are not reimbursed under health plans, or immunizations offered in the workplace) are if they are validated by a health care professional and included in the EHR. For example, if a patient receives an immunization at a site not in the care delivery system, but has valid proof that it was received and that immunization is reviewed, validated, and documented in the EHR by the healthcare professional, it is currently unclear whether that data would be considered "suitable" for FDA regulatory purposes. Following the current guidance, this data source would appear to be unsuitable as RWD. Nonetheless, this represents care in the real world and an important data point in the patient's care journey that may be relevant to the study for regulatory purposes.

Data Linkages and Synthesis

We note a general absence of discussion of data standards in this guidance. We encourage FDA to collaborate with ONC in its use and improvement of Fast Healthcare Interoperability Resources (FHIR) to address the technical standards for data exchange.[6] Additionally, we encourage FDA to collaborate with HL7 FHIR and their Accelerator projects, in particular the Vulcan Project, which focuses on collaborations to support data standards and data sharing standards for clinical research.[7] Further, we reiterate that FDA should seek to align its standards with the USCDI in order to ensure consistent capture of any recommended data elements.

Distributed Data Networks

FDA discusses the use of Common Data Models (CDM). We recommend an additional use of CDMs, in that FDA guidance should ask study sponsors to provide data that would allow for third-party validation through a CDM-driven network, such as the Sentinel Initiative. This would provide the metadata that would be needed to help ensure adherence to the FAIR Data Principles[8] in RWE generation, or at least allow for certain biases to be surfaced.

Computable Phenotypes

[6] https://www.healthit.gov/topic/standards-technology/standards/fhir-fact-sheets.
[7] http://www.hl7.org/vulcan/
[8] https://www.go-fair.org/fair-principles/

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FDA's discussion on computable phenotypes appears to suggest that associated metadata elements already exist. We note that this is, in fact, an open area of work with many different groups developing phenotype libraries with various types and quality of metadata. Several groups, including the Covid-Knowledge Accelerator project[9] and the Mobilizing Computable Biomedical Knowledge (MCBK) initiative[10] are collaborating to identify such metadata standards. A set of metadata categories has even been published.[11]

Similarly, the specifications for a standard "computer-processable format" of the phenotype definition does not currently exist. In lieu of a standard coding language, will the code used to operationalize the definition in the source database be sufficient? Should investigators represent and share phenotypes using emerging standards (e.g., CQL) even though they may not be fully robust to describe all existing phenotype definitions? A recent desiderata[12] for representing and sharing phenotype definitions in libraries suggests that "implementation tooling" that can automatically translate abstract phenotype definition components into a computable formats for target systems will improve portability. We argue that this increased portability will also lead to increased transparence and re-use – improving the speed with which RWE can be generated. FDA should acknowledge that there are not consistent methodologies for representing and sharing computable phenotypes and suggest a road map or standards development organization to move toward standardized computable representation for computable phenotypes.

Missing Data: General Considerations

FDA discusses cases of missing data. Indeed, "missingness" is one of the most common and problematic features of RWD data sets, especially those derived from EHR data. We recommend that FDA provide guidance and better clarity on standards and definitions for documenting, recording, and reporting data missingness in data used by the FDA for regulatory purposes. Definitions of missingness have been used effectively in clinical epidemiological research abroad to help set standards for how missingness is evaluated.[13]

Validation: General Considerations

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[9] https://gps.health/covid-19-knowledge-accelerator-coka/

[10] https://mobilizecbk.med.umich.edu/

[11] Alper, B. S., Flynn, A., Bray, B. E., Conte, M. L., Eldredge, C., Gold, S., Greenes, R. A., Haug, P., Jacoby, K., Koru, G., McClay, J., Sainvil, M. L., Sottara, D., Tuttle, M., Visweswaran, S., & Yurk, R. A. (Accepted/In press). Categorizing metadata to help mobilize computable biomedical knowledge. *Learning Health Systems*. https://doi.org/10.1002/lrh2.10271

[12] Chapman M, Mumtaz S, Rasmussen LV, Karwath A, Gkoutos GV, Gao C, Thayer D, Pacheco JA, Parkinson H, Richesson RL, Jefferson E, Denaxas S, Curcin V. Desiderata for the development of next-generation electronic health record phenotype libraries. Gigascience. 2021 Sep 11;10(9):giab059. doi: 10.1093/gigascience/giab059. PMID: 34508578; PMCID: PMC8434766.

[13] Pedersen AB, Mikkelsen EM, Cronin-Fenton D, Kristensen NR, Pham TM, Pedersen L, Petersen I. Missing data and multiple imputation in clinical epidemiological research. Clin Epidemiol. 2017 Mar 15;9:157-166. doi: 10.2147/CLEP.S129785. PMID: 28352203; PMCID: PMC5358992.

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FDA writes that studies using EHR and medical claims data sources should include conceptual definitions for important study variables, from which operational definitions should be developed. While it notes later in the guidance that key variables used to select the study population should be validated, we recommend that FDA explicitly recommend descriptions of how the operational and conceptual definitions are linked in the validation process. For example, during the validation process is the conceptual definition used during a manual review process to validate the operational definition? Did linked data sources used for validation (i.e., by comparing algorithm performance to a patient registry) use the same conceptual definition as described in the study? This linking of conceptual and operational definitions is often missing in the phenotyping literature, for example, yet it is critically important to understanding the applicability of evidence for patients during clinical care.[14]

Because the performance of an operational definition is dependent on various factors, FDA also recommends assessing the performance of operational definitions in an adequately large sample of the study population as part of the proposed study, using justified sampling methods (e.g., random sampling, stratified sampling). It continues that the quality of prior studies used to establish sensitivity, specificity, and predictive values should always be evaluated. However, we observe that not all fields have an adequate sense for how well the performance of certain algorithms generalize to other data sources. The existing literature on phenotyping, to continue the example, supports that most algorithms require at least some changes to enable the algorithm to run in the new data source (i.e., "localization"), but it is unclear what the impact of these effects on the validity of the algorithm in the new data source will be. At a minimum, we recommend some form of validation on the new data source to confirm similar performance.

Data Quality During Data Accrual, Curation, And Transformation Into The Final Study-Specific Dataset

FDA writes that while it does not endorse any particular set of guidelines or checklists, researchers should evaluate the completeness, accuracy, and plausibility of the data, including verifying data against its original source and conforming to consensus-based data standards, where applicable. To aid in this effort, FDA should promote a standardized way of reporting on metadata associated with the dataset used for the RWE used in the sponsor study. There are currently no industrial standards with regards to how to evaluate the post-implementation performance of RWE-driven products. FDA should use this guidance opportunity to promote a set of evaluation standards that should be complied with when evaluating how the RWE could be generalized to other populations the product would be applied to. This set of standards should also include metadata that could be used to evaluate the compliance to FAIR Data Principles and health equity. This would include performance, given the various population characteristics and other data characteristics pre-defined as important to be checked.

Characterizing Data Provenance

[14] Sabb FW, Burggren AC, Higier RG, Fox J, He J, Parker DS, Poldrack RA, Chu W, Cannon TD, Freimer NB, Bilder RM. Challenges in phenotype definition in the whole-genome era: multivariate models of memory and intelligence. Neuroscience. 2009 Nov 24;164(1):88-107. doi: 10.1016/j.neuroscience.2009.05.013. Epub 2009 May 18. PMID: 19450667; PMCID: PMC2766544.

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FDA rightly notes that format and provenance of EHR and medical claims data can vary significantly across health care entities. We recommend additional guidance that utilizes concrete use cases of how data provenance can be reported and classified. Given the multiple origins of digital healthcare data within and outside of the healthcare delivery system, it is important that FDA provide guidance specific on provenance for EHR and claims data. For example, some EHR data may originate from personal wearable devices. The provenance of such data must be addressed when used for regulatory purposes.[15]

As for the data accrual process that FDA recommends be included in automated data quality reports, we note that this component of data quality assessment can be highly technical and require bioinformatics expertise. We urge FDA to collaborate with the Office of the National Coordinator for Health IT (ONC) to collaboratively co-develop guidance for technical standards for provenance evaluation and documentation.

We additionally recommend that the data quality reports include which data source research sites are drawing from within their EHR. For example, there are numerous data model differences present between Clarity[16] and Caboodle[17] that have profound impacts on data interpretation and fitness for purpose.

Documentation of Data Management Process

FDA writes that all manual and automated data retrieval and transformation processes should be thoroughly assessed from data collection, through writing of the final study report to ensure data integrity. We recommended that FDA provide guidance and a template that structures how data quality assessments must be reported, as well as the criteria upon which reported data quality assessment dimensions and methods will be scored and evaluated. Given that the process for data quality evaluation will be novel for RWD/RWE, the FDA should build in a scheduled review process that iteratively shares what it is learning about data quality evaluation. This will help to create a learning center/culture for data quality evaluation and assessment.[18,19]

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[15] Curcin V. Embedding data provenance into the Learning Health System to facilitate reproducible research. Learn Health Syst. 2016 Dec 27;1(2):e10019. doi: 10.1002/lrh2.10019. PMID: 31245557; PMCID: PMC6516719.

[16] https://ehealth.connect-care.ca/epic-systems/epic-analytic-tools/clarity

[17] https://ehealth.connect-care.ca/epic-systems/epic-analytic-tools/caboodle

[18] Callahan T, Barnard J, Helmkamp L, Maertens J, Kahn M. Reporting Data Quality Assessment Results: Identifying Individual and Organizational Barriers and Solutions. EGEMS (Wash DC). 2017 Sep 4;5(1):16. doi: 10.5334/egems.214. PMID: 29881736; PMCID: PMC5982990.

[19] Kahn MG, Brown JS, Chun AT, Davidson BN, Meeker D, Ryan PB, Schilling LM, Weiskopf NG, Williams AE, Zozus MN. Transparent reporting of data quality in distributed data networks. EGEMS (Wash DC). 2015 Mar 23;3(1):1052. doi: 10.13063/2327-9214.1052. PMID: 25992385; PMCID: PMC4434997.