AMA
AMERICAN MEDICAL ASSOCIATION

JAMES L. MADARA, MD
EXECUTIVE VICE PRESIDENT, CEO

ama-assn.org
t (312) 464-5000

December 20, 2019

The Honorable Stephen Hahn, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Draft Guidance for Clinical Decision Support Software [Docket number FDA-2017-D-6569]

Dear Commissioner Hahn:

On behalf of the physician and medical student members of the American Medical Association (AMA), I appreciate the opportunity to provide comments on the Draft Clinical Decision Support Software Guidance (Draft 2019 Guidance). The AMA appreciates the U.S. Food and Drug Administration's (FDA) efforts to provide clarity on the scope of the FDA's oversight of clinical decision support software (CDS) intended for health care professionals (HCP), patients, or caregivers. AMA understands the challenges associated with interpreting the scope of the Agency's authority to regulate CDS based on the 21st Century Cures Act amendments to the Food, Drug, and Cosmetic Act (FDCA). However, we strongly urge the FDA to affirmatively address a number of issues that the AMA has raised previously in response to the Agency's work on Software as a Medical Device (SaMD), including establishing standard terminology and definitions, and reconsideration of the use of the International Medical Device Regulators Forum (IMDRF) risk framework. In addition, key components of the Draft 2019 guidance related to HCPs and independent review may undermine safety, efficacy, and equity and should be reevaluated.

Standard and Consistent Terminology

The AMA strongly urges the FDA to develop a glossary of terms and definitions for artificial intelligence (AI) (which the AMA describes as augmented intelligence)[1] and related terms and methods. We further urge the FDA to prioritize collaboration with sister agencies to ensure government-wide consistency in the use of terms and definitions associated with regulation of software and AI-based products. The lack of consistent and shared terms and definitions across federal and state health care regulatory bodies (FDA and the Federal Trade Commission (FTC), state medical boards and health insurance commissions, for example) invites confusion and difficultly complying with relevant laws and requirements, adding another layer of complexity to an already challenging and rapidly evolving environment. FDA has issued a number of documents in the past year and a half, and many employ different terms to discuss AI, machine learning, deep learning, and other relevant terms, often with meanings and definitions that have to be

[1] The AMA considers both assistive and autonomous AI systems as augmenting human decision-making and patient care. Also, current AI systems are considered narrow AI systems with specific applications and intended uses as opposed to general AI systems.

inferred. Furthermore, the Agency continues to use evolving and, in some cases, inexact definitions of AI systems. Federal agencies should strive to avoid the confusion that has occurred in the digital health arena where, for example, the lack of a standard and consistent definition of telehealth among state regulators, federal health care programs, and commercial payers has created widespread confusion and difficulty in scaling education, adoption, and compliance programs.

Cross-agency coordination and harmonization on this work would be preferred to ensure consistency across federal regulatory bodies and provide guidance to state-level regulators. However, if this cannot be achieved in a timely fashion, we strongly urge the FDA, at a minimum, to consider incorporating the work of a standards-setting body that has developed definitions into the Agency's regulatory proposals. Ideally, this would include incorporation of standards that can be used cross-sectoral to avoid conflicting meanings when services and products developed utilizing such systems have different applications and uses, but intersect with health care uses or settings.

21st Century Cures Act: CDS De-Regulation and "Enabling an HCP to Independently Review"

Section 3060 of the 21st Century Cures Act of 2016 (Cures Act) removed the FDA's authority to regulate certain CDS that meets the definition of medical device software, including where the CDS is intended for "the purpose of enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional relies primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient." During congressional consideration of the Cures Act, the AMA did not support initial versions of Section 3060 that would have removed the entirety of FDA's oversight authority over CDS. To avoid complete deregulation and subject patients to undue risk of harm, the AMA, patient groups, and select members of industry advocated that language should be included that would, at a minimum, ensure that the FDA retained oversight authority over black-box CDS as specified in Section 520(o)(1)(E)(iii). To that end, the above "HCP independent review" language was added to Section 3060. However, this was a compromise that creates a challenge as it could invite developers to characterize their CDS as assistive and fail to provide the basis for a clinical diagnosis or treatment decision regarding an individual patient. This exception is difficult to implement as the intended use of CDS is to influence clinical decision-making while reducing HCP cognitive burden.

The above problem is pronounced in the context of more advanced algorithms and methods. With rule-based CDS software, the rationale for the output and relevant clinical endpoints are more likely to be evident or available so that the end-user is able to assess the basis of the recommendation. However, where CDS has been developed utilizing machine learning alone or in combination with other methods and systems such as computer vision and natural language processing, the basis of the recommendation would lack transparency unless developed or subsequently validated to align with clinical endpoints that physicians would utilize to diagnose or treat a patient. While there are examples[2] where a developer has utilized machine learning and ensured clinical endpoints align with clinical practice guidelines and current clinically relevant endpoints utilized in practice, this is not adequately specified in the guidance.) While it is possible to conduct validation to verify that CDS outputs align with clinical endpoints physicians would typically rely upon, this was not specified in the guidance. This must be explicit and minimally required for regulated products *as well as* CDS that is not subject to FDA oversight.

[2] IDx-DR is regulated by the FDA as an autonomous SaMD system, but nonetheless was validated against a number of clinical endpoints including those relied upon by ophthalmologists to render a clinical decision.

Furthermore, the AMA does not agree that CDS utilizes certain AI systems and methods such as, but are not limited to, machine learning or deep learning, fall outside of FDA oversight. The Draft 2019 Guidance states "that the complexity or proprietary nature of the algorithm is not the distinguishing factor as much as the ability of the healthcare provider to confirm the output independently, using the same inputs and basis." The draft guidance proposes that non-device CDS software functions should describe: (1) the purpose or intended use of the software function; (2) the intended user; and, (3) the inputs used to generate the recommendation and the basis for rendering a recommendation. The complexity and/or proprietary nature of the CDS is exactly what would limit an independent review of the basis of the output which is required by law to be exempt from regulation. However, the AMA welcomes the opportunity to discuss with the Agency examples of CDS that utilize machine learning or deep learning that the FDA has concluded would provide the statutorily required basis to aid a HCP's independent assessment of the recommendation. In the case of proprietary algorithms, there is no ambiguity with regard to whether these are subject to regulation under the law. By definition proprietary algorithms are intentionally black box and, thus, subject to FDA regulation. Finally, the AMA strongly urges that the FDA clearly specify that the information needed to discern the basis of the output must be available at the clinician level, and that peer review publication would not be sufficient to provide the requisite level of transparency required by statute.

The FDA also proposes to exercise enforcement discretion for CDS functions used by healthcare professionals that inform clinical management of non-serious conditions when the user is unable to independently review the basis of the recommendation. The draft guidance uses the IMDRF risk framework to define non-serious conditions as those "situations or conditions where an accurate diagnosis and treatment is important but not critical for interventions to mitigate long term irreversible consequences on an individual patient's health condition or public health." We are concerned that this provision would lead to the proliferation of CDS tools for "non-serious conditions" that are faulty, inaccurate, and without validation, potentially leading to patient harm. We strongly urge the FDA to revisit this component of the Draft 2019 Guidance. At a minimum, we urge FDA to work with FTC to issue consumer protection guidance, ensuring that developers understand that they are required to ensure the safety, efficacy, and equity of such tools as the baseline for adhering to consumer protection laws.

Application of International Medical Device Regulators Forum Risk Categorization

The AMA applauds the significant time and effort that the FDA has dedicated to drive international consistency and harmonization for SaMD oversight through the IMDRF. However, the AMA continues to have serious concerns that the current framework does not: (1) account for varying levels of autonomy; (2) provide intuitive or clear distinctions between "inform" and "drive;" nor, (3) address heightened risk of certain methods or systems such as continuous learning systems that have "unlocked" learner algorithms. We strongly urge the FDA work with the IMDRF to address these three issues before application and use in FDA guidance documents. We further urge FDA to consider providing opportunity for public comment on the IMDRF framework, as, to date, no such opportunity has been provided other than on its incorporation as part of larger FDA regulatory proposals. In addition, the AMA welcomes the opportunity to provide an overview of key concepts and terms including possible definitions of "inform" and "drive" that the AMA's Digital Medicine Payment Advisory Group (DMPAG) is actively considering. The DMPAG has convened a workgroup of physicians with expertise in the ideation, design, development, validation, and deployment of AI systems in health care to discuss these issues in greater

depth in order to provide recommendations to align payment and regulatory terms, as well as heuristics to provide standard descriptions of such systems.

Patient and Caregiver CDS

In addition to CDS used by health care providers, the Draft 2019 Guidance addresses CDS functions used by the patient or caregiver, but the FDA's enforcement discretion will not be as broad as for healthcare professionals. As a result, CDS functions used by patients or caregivers that inform clinical management of serious or critical conditions will remain under regulatory oversight. The AMA strongly supports the foregoing provision of the draft guidance. However, the FDA proposes to maintain enforcement discretion for CDS functions used by patients or caregivers that inform clinical management of non-serious conditions when the user can independently review the basis of the recommendation. Again, while the AMA understands the FDA's limited resources, we have significant concern that this will invite a proliferation of patient CDS that is not safe, efficacious, or equitable. As a result, we urge the FDA to work with the FTC to ensure developers have additional clarity with regard to the standards that should be met to avoid violation of consumer protection laws.

The AMA appreciates the opportunity to provide comment. If you have questions, please contact Shannon Curtis, Assistant Director, Federal Affairs at shannon.curtis@ama-assn.org.

Thank you.

Sincerely,

James L. Madara, MD