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By electronic submission

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RE: UCSF CENTER FOR DIGITAL HEALTH INNOVATION'S COMMENTS ON FDA'S DRAFT SOFTWARE PRECERTIFICATION PROGRAM WORKING MODEL, FILE NO. FDA-2017-N-4301-0001

Dear Mr. Patel,

The University of California, San Francisco's Center for Digital Health Innovation submits these comments on the Food and Drug Administration's draft Software Precertification Program Working Model, issued April 24, 2018. The University of California, San Francisco (UCSF) is a worldwide leader in health care delivery, discovery, and education. Consistent with this public imperative, UCSF invests heavily in developing a variety of health information technology, innovation, and management resources and best practices to give health care providers and patients,[1] researchers and scientists, educators and students the digital diagnostic and therapeutic tools such as software as a medical device and interoperability to succeed in this rapidly evolving digital health age. We thank you for the opportunity to provide these comments.

The Food and Drug Administration's Center for Devices and Radiological Health (FDA) invites public comment on the draft Working Model and questions on appraising a software developer's capabilities, determining the appropriate level of review, streamlining the pre-market review process, and assessing and reporting real-world performance. We appreciate the considerable work that the FDA has devoted to this draft in order to improve innovation, access, and use of software as a medical device across the health care ecosystem. In the comments below, UCSF's Center for Digital Health Innovation focuses on the area of real-world performance. We discuss the

[1] For brevity, these comments refer to "patient" and "care," given that many federal programs and initiatives are rooted in a clinical or medical model. Health and health care, however, embrace more than clinical settings and extend well beyond clinical treatment of episodes of illness and exclusive dependency on professionals. Any effort to improve patient and family engagement must include terminology that also resonates with the numerous consumer and community perspectives not adequately reflected by medical model terminology. For example, people with disabilities and others frequently refer to themselves as "consumers" or merely "persons" (rather than patients). Similarly, the health care community uses the terminology "caregivers" and "care plans," while the independent living movement may refer to "peer support" and "integrated person-centered planning."

significance of collecting and evaluating real-world performance data, what data to collect and evaluate, who to involve, and where to share and publish the results. We also recommend adding "Interoperability" as a core principle of excellence, consistent with Congress's findings in the 21st Century Cures Act, and lift up a model software precertification notice to promote transparency and understanding across all end-users and the general public.

EXPERTISE OF UNIVERSITY OF CALIFORNIA, SAN FRANCISCO AND UCSF'S CENTER FOR DIGITAL HEALTH INNOVATION

UC San Francisco is a worldwide leader in health care delivery, discovery, and education. In recent years, we have invested heavily in developing the information technology resources to help health care providers, patients, educators, scientists, and students have the interoperability and tools needed to succeed in the rapidly evolving digital age. UCSF's medical centers consistently rank among the nation's top hospitals, according to U.S. News & World Report, and see approximately 43,000 hospital admissions and 1.2 million outpatient visits annually, including care of the county's underserved and veteran populations.

UCSF focuses on solving real and important problems at national, regional, and global levels. UCSF's own scope extends beyond tertiary/quaternary care at UCSF facilities, to our level one trauma center at Zuckerberg San Francisco General Hospital, the county hospital and safety net hospital for San Francisco; to the San Francisco Veterans Affairs Medical Center; and to our accountable care organizations (ACOs) including community hospitals and clinics across the Bay Area. Additionally, through UC Health, we have access to 15 million patient health records at six academic medical centers across the State of California, representing an incredibly diverse set of individuals and approximately one third of California's population in the world's seventh largest economy. Therefore, we represent the full continuum of healthcare, with access to patient and population-level data on myriad disease conditions and patient demographics.

We have played a seminal role in developing precision medicine, an emerging field that aims to harness vast amounts of molecular, clinical, environmental and population-wide data to transform the future of health diagnosis, treatment and prevention for people worldwide. Indeed, UCSF's policy and research leadership helped stimulate the nation's Precision Medicine Initiative, urgently moving forward under the 21st Century Cures Act to improve care and health for individuals across the nation. UCSF research has spawned more than 185 startups, including pioneers Genentech and Chiron, and helped establish the Bay Area as the nation's premier biotech hub.

In 2013, UCSF founded its Center for Digital Health Innovation (CDHI), which partners with technology companies to solve real-world health problems and speed the implementation of innovation into everyday health care. CDHI is renowned for its thought leadership in digital health. For example, CDHI partners with Intel and GE to build deep learning prediction algorithms to be leveraged behind the scenes and at the point of care by frontline providers. This program, called **SmarterHealth**, integrates our evidence-based research and clinically rigorous approaches to digital health innovation into a collaborative approach with leading industry partners to build

infrastructure, processes, and products that address high priority, real-world problems in care delivery. SmarterHealth creates methodologies and tools to access, harness, and annotate multi-modal data in a scalable and repeatable process using advanced analytics and deep learning (artificial intelligence approaches).

CDHI also creates tools and services that allow developers to create, test, and distribute apps and decision-support algorithms in a scalable, EHR-agnostic manner. Currently, our work focuses on enabling the ecosystem of innovative health apps and open application programming interfaces (APIs) that improve workflows, care quality, and patient engagement by creating true health data interoperability.

Similarly, our UCSF-Stanford **Center of Excellence in Regulatory Science and Innovation (CERSI)** was the first regulatory science and innovation center on the West Coast. Collaborating with the U.S. Food and Drug Administration, the three partners work on projects that promote the emerging field of regulatory science—including innovative research, education, outreach, and scientific exchange—together with foundations and commercial entities interested in the development of FDA-approved medical products.

The Center for Digital Health Innovation is just one among many centers that UCSF has dedicated to helping the nation reach its digital health imperatives. For example, the Institute for Computational Health Sciences (ICHS) under Dr. Atul Butte leads nationally renowned work to advance precision medicine and big data. The Center for Vulnerable Populations is known nationally and internationally for innovative research to prevent and treat chronic disease in populations for whom social conditions often conspire to promote various chronic diseases and make their management more challenging. The Social Interventions Research and Evaluation Network (SIREN) at the Center for Health and Community is working to integrate social and environmental determinants of health. The Center for Clinical Informatics and Improvement Research (CLIIR) under Dr. Julia Adler-Milstein leads national research on use of EHRs and other digital tools to improve health care value. We bring the depth and breadth of these and many other efforts to bear in our comments below.

REAL-WORLD PERFORMANCE DATA—LESSONS FROM THE FIELD FOR THE SOFTWARE PRECERT PROGRAM

We appreciate the considerable work that the FDA has devoted to this draft in order to improve innovation, access, and use of software as a medical device (SaMD) across the health care ecosystem. We focus below on real-world performance and discuss the significance of collecting and evaluating real-world performance data, what data to collect and evaluate, who to involve, and where to share and publish the results.

A. The significance of collecting and evaluating real-world performance data

The Software Precertification Program precertifies the developer of the software as a medical device based on the developer's organizational excellence, and depending on the eligible device's level of risk, allows it to proceed to market without a pre-market submission or with streamlined pre-market review. This regulatory approach shifts the

timeframe for traditional pre-market evaluation, but grounds it with real-world performance data in real-world contexts.

The collection and crowdsourcing of real-world performance data become key for the adequacy of regulatory review and iterative development of devices. This post-market complement allows the developer, the FDA, and the consumer to answer, "is this SaMD product reliably and accurately performing the functions that the developer intends and the user expects it to perform, and does the real-world performance substantiate this?" After all, collecting, analyzing, evaluating, and learning from real-world performance data are critical characteristics of an excellent, high-performing organization. Without such transparent and structured real-world performance data, we worry that "Precertification" would instead be a meaningless branding distinction.

Indeed, real-world performance data may be the most critical aspect of the Precertification process, both to verify the safety and efficacy of the software as a medical device, but also to frame and test iterative improvement and innovation in SaMD products. **As such, all Program participants at all levels must collect and publicly report their real-world performance data, and participation in real-world performance data collection and reporting must be a prerequisite of PreCert Program participation.** In the absence of the usual pre-market clinical trials to demonstrate efficacy, real-world performance data are essential. There are a number of early examples of algorithms, created with standardized datasets, which do not perform as well in validation studies in the clinical environment using real-world data.

While all Program participants should collect and report real-world performance data, what a participant must collect and report might be tailored or scaled depending on a particular SaMD's functions, relative risks, and potential harms. For example, the FDA could allow SaMD with minimal risk and potential harm to report real-world performance data over shorter timeframes. There is precedent for such an approach when appropriate. For example, healthcare providers must regularly conduct risk assessments of how their electronic health records protect the security and privacy of their patients' health information, but an individual provider may tailor its risk assessment to its respective circumstances and environment. [2]

In this way, one size of pre-market review need not (and cannot) fit all. Each SaMD product will have a different set of intended functions and potential consequences. Incorporating precertification and real-world performance data for lower risk software still allows and expects each product to "show its math" on its essential function(s) and outcomes in the real world, and how the developer and software are ensuring that the function is accurately and reliably performed and measured. By requiring real-world performance data submissions for all, having two levels of precertification becomes feasible and safer for patients by creating a pathway for even small companies to be able to enter the market and innovate.

Lastly, we applaud the FDA for proposing that data no longer come just from sporadically reported information at the time of a bad outcome, but rather to insist on proactive data collection from real-world health data sources and from instrumentation

[2] Office for Civil Rights, U.S. Department of Health and Human Services, Guidance on Risk Analysis Requirements under the HIPAA Security Rule (July 14, 2010), available at https://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/administrative/securityrule/rafinalguidancepdf.pdf.

of the SaMD product itself. The instrumentation is critical, because not only is it a source of user data to learn about product efficacy and performance, but a company properly instrumenting their product is demonstrating an industry best practice, demonstrating intent to learn about how their product is performing.

B. What real-world performance data to collect and evaluate

The draft Working Model identifies various types of real-world performance data, including real-world health data, user experience data, and product performance data. One might be inclined to identify product performance data as the most important of the three, but we suggest instead that each is important for its respective purpose. On the cusp of a new regulatory approach in a new and rapidly evolving digital health ecosystem, it is especially important to collect all three types of real-world performance data in order to be able to evaluate interactions among the three, e.g. user experience and product performance. We applaud the FDA for thinking about and including these three data types, for collectively they provide an important overall view of SaMD in practice.

Product performance data are crucial for evaluating real-world performance. Does the SaMD product reliably perform the functions that developer and user expect it to perform? Are there any unintended consequences? Is the SaMD product representing data accurately? Does it have any security flaws? These are basic and essential. Products that cannot meet this standard are likely not safe to use in healthcare.

Once we know that the SaMD is safe and performs the functions we expect, we also want to know whether it is usable and integrates well with workflows, and whether it is actually making any difference in clinical care and outcomes. Real-world performance should also collect user experience data (e.g. usage statistics such as clicks, downloads, sessions), and real world health data on actual clinical performance, both clinical processes (for example, with a diabetes app, the number of times blood sugar guidance is used by patients) and clinical outcomes (with this same app, whether usage of the app produces better blood sugars).

Note that assessing outcomes can depend upon and vary with the predicate health goal. Patients and providers may not articulate health goals in the same way; the doctor may be looking for better blood sugars, and the patient may be looking for less fatigue or an end to blurry vision.

The FDA and other stakeholders should also consider how to collect and report data about context and provenance regarding the various uses and performance of the software. Examples include the version of the software, the type of clinical setting, the type of electronic health record, the type of user, perhaps the patient's condition or diagnosis or the type of use case. Software and its real-world performance do not exist in a vacuum, and real-world performance data alone may not capture all factors or interactions relevant to the measured performance. Human-user interventions or errors are obvious examples. Context will affect performance in ways the FDA and stakeholders should want to measure and understand. This information, in turn, will help users, vendors and the FDA understand how innovation can be catalyzed in ways that meet many sites' needs.

All data should be collected in a trustworthy manner, so they can properly inform vendors' and purchasers' decisions about whether and how to partner to improve products or to undertake deeper experiments (such as A/B testing under human subjects protection). In this way, trustworthy collection of real world performance data can support rapid innovation, iteration, and learning.

C. Who to involve in collecting and evaluating real-world performance data, and where to share and publish the real-world performance data and results

Real-world performance data should be collected from and shared across the range of stakeholders and care settings, including health systems, clinics, and clinicians; software developers and EHR vendors; patients; health insurers and other payors; committees working to identify and apply best practices for selecting and integrating software as a medical device (sometimes called digital diagnostic and therapeutic committees); and the FDA. This not only ensures post-market monitoring and evaluation across the range of relevant care settings and real-world contexts, but it also actively engages each of them, incorporates their relevant data and perspectives, and cultivates shared, informed decision-making about the software as a medical device and its impact. This is necessary for effective performance measurement across iterative cycles in real contexts.

CDHI RECOMMENDS ADDING "INTEROPERABILITY" TO THE SOFTWARE PRECERTIFICATION PROGAM'S PRINCIPLES

We urge the FDA to add "Interoperability" as a sixth core principle of excellence to the Software Precertification Program.

In the 21st Century Cures Act, which addressed the FDA's responsibilities to improve medical device innovation,[3] Congress also declared "interoperability" a national priority and imperative, to assure electronic access, exchange, and use of health information, nationally and locally.[4] Clearly, interoperability of software as a medical device is no less important than product quality, patient safety, clinical responsibility, cybersecurity protection, and proactive culture. Indeed, without interoperability, the other principles become moot in a digital health ecosystem.[5]

The FDA could easily adopt the 21st Century Cures Act's principle and definition of interoperability:

> INTEROPERABILITY.—The term 'interoperability', with respect to health information technology, means such health information technology that—

[3] 21st Century Cures Act, §§ 3051-3060.
[4] 21st Century Cures Act, § 4003 (adding 42 U.S.C. § 300jj-12(b)(2)(B)(i), (c)(2)).
[5] The FDA has already identified the importance of interoperability in its guidance to the industry and FDA staff on Design Considerations and Premarket Submission Recommendations for Interoperable Medical Devices, published September 6, 2017.

> (A) enables the secure exchange of electronic health information with, and use of electronic health information from, other health information technology without special effort on the part of the user;
> (B) allows for complete access, exchange, and use of all electronically accessible health information for authorized use under applicable State or Federal law; and
> (C) does not constitute information blocking as defined in section 3022(a).[6]

Regarding exchange and use of electronic health information "without special effort on the part of the user," Congress specifically highlighted the importance of open application programming interfaces (APIs),[7] and the FDA should expect software as a medical device to use and integrate with open APIs as well.

A MODEL NOTICE PROVIDING KEY, STANDARDIZED INFORMATION ABOUT THE SOFTWARE AS A MEDICAL DEVICE WOULD GREATLY HELP ALL USERS UNDERSTAND, USE, AND COMPARE THE PRODUCT

CDHI recommends that the FDA develop a model software precertification notice and require Program participants to publish it for each product and iteration or version of the software as a medical device. The model notice would provide standardized information about key elements of the software, and would provide the FDA, the public, and all end users an objective, user-friendly description and objective comparison across products on key items based on pre-market assessment and post-market real-world evidence and experience.

Standardizing the elements and structure of reported data helps consumers, users, and health systems understand the information being reported and makes the information usable in the real world. By requiring all developers to provide the notice and information, it becomes an informative pre-competitive tool, where developers compete on the features and quality of their software rather than the packaging or secrecy of important product information.

Other agencies have used a model notice for similar purposes. For example, the Office of the National Coordinator for Health Information Technology developed a Model Privacy Notice as a voluntary, openly available resource designed to help health technology developers provide clear notice to consumers about what happens to their digital health data when the consumer uses the developer's product.[8] A model notice for software as a medical device should likewise cover what happens to digital health data when one uses the developer's product, but should cover other key elements as well.

ONC's Model Privacy Notice covers, for example, how the developer uses the data internally, whether and how the developer shares or uses the data externally, whether and how the developer stores and encrypts data, and how the end user can use the data. For a model software precertification notice, the FDA should cover these important

[6] 21st Century Cures Act, § 4003(a)(2).
[7] Section 4002 of the 21st Century Cures Act requires that certified EHR technology "has published application programming interfaces and allows health information from such technology to be accessed, exchanged, and used without special effort through the use of application programming interfaces or successor technology or standards . . . ."
[8] Office of the National Coordinator for Health Information Technology, "2018 Model Privacy Notice," available at https://www.healthit.gov/sites/default/files/2018modelprivacynotice.pdf.

security and privacy elements, as well as important, standard elements at the pre-market stage (such as elements on quality, safety, and clinical outcomes) and important, standard elements with post-market performance data. Pre-market information could include intended uses and users, integration with open APIs (read and write), whether the SaMD supports single sign-on, and types and levels of pre-implementation configuration and content required before real-world use. Post-market performance data could include performance metrics (both clinical process and clinical outcomes) and quality and safety metrics. The notice would also help all stakeholders keep up with the turnover in technology companies' software, versions, acquisitions, market departures, etc. Such published notices could be a condition of participation in the Program, at least annually and more frequently with any update in any element reported in the notice.

Conclusion

Thank you for the opportunity to provide these comments on the draft Working Model. In general, we think that the Working Model is on the right track and that the FDA is thinking about the right issues in the right ways. UCSF's Center for Digital Health Innovation looks forward to working with the FDA, developers, providers, consumers, and other stakeholders across the nation to improve innovation and use of software as a medical device across the digital health ecosystem. If you have any thoughts or questions about these comments, please contact Mark Savage at Mark.Savage@ucsf.edu.

Sincerely,

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