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By electronic submission

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RE: UCSF CENTER FOR DIGITAL HEALTH INNOVATION'S COMMENTS ON VERSION 1.0 OF 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, version 1.0, issued January 7, 2019. The University of California, San Francisco (UCSF) is a worldwide leader in health care delivery, discovery, and education, with a mission of "Advancing Health Worldwide." 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 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 version 1.0. We appreciate the considerable work that the FDA has devoted to the Software Precertification Program and this revised working model in order to improve innovation, access, and use of software as a medical device (SaMD) across the health care ecosystem. In the comments below, UCSF's Center for Digital Health Innovation focuses on the area of real-world performance. Based upon our real-world experience, **we renew our recommendation to add four**

[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."

subdomains to the FDA's framework for real-world performance analytics, namely "real-world usage," "workflow," "interoperability," and "universal design." Congress identified interoperability as a national priority in the 21st Century Cures Act, and we highlight interoperability analytics based on groundbreaking work in the National Quality Forum's Interoperability Measurement Framework. We recommend, too, that the FDA **require instrumenting of SaMD products to collect and analyze real-world performance data and analytics**, without precluding use of alternative data sources as well. Lastly, we iterate our prior recommendation that the **FDA develop and use a model software precertification notice for products to provide transparency**, with examples of why such transparency is so important to stakeholders and the public.

I. 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, researchers, innovators, educators, 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 California, representing an incredibly diverse set of individuals and approximately one third of California's population in the world's fifth largest economy. Therefore, we represent the full continuum of healthcare, with access to patient and population-level data on myriad disease conditions and 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. 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.

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).

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 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.

In conjunction with CERSI, UCSF and CDHI recently launched a national collaboration – the Accelerated Digital Clinical Ecosystem (ADviCE) – that is focusing on implementation and evaluation of software as a medical device in clinical care. A collaboration initially among UCSF, leading national health systems, SaMD innovators, payers, and consumers, ADviCE is aligned with the Precertification Program's near and longer term needs. Specifically, ADviCE aims to identify best practices around use of digital health tools – particularly those which have been precertified – in clinical care delivery and in monitoring the effectiveness of these tools in clinical practice using real world data, and then to launch a 'collaborative community' that will apply them to software as a medical device. ADviCE collaborators have provided important insights around the role of real-world performance analytics, evaluation, and regulation in the deployment of software as a medical device, insights which have helped frame our comments below.

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.

II. REAL-WORLD PERFORMANCE DATA AND ANALYTICS—RECOMMENDATIONS TO IMPROVE THE FDA'S FRAMEWORK OF KEY DOMAINS AND SUBDOMAINS

CDHI appreciates the considerable work that the FDA has devoted to this revision in order to improve innovation, access, and use of software as a medical device across the health care ecosystem. Our prior comments have recommended a few additional subdomains to improve the FDA's framework of key domains and subdomains to measure real-world performance analytics. We acknowledge the FDA's stated intent to hold revision of the real-world performance domains and subdomains until the FDA concludes testing in 2019 (p. 41), but we continue to believe that these subdomains are especially important and warrant testing with the FDA's other subdomains in 2019. Accordingly, we renew our recommendation to add four subdomains to the FDA's framework for real-world performance analytics, namely "real-world usage," "workflow," "interoperability," and "universal design." We use Figure 8 and Appendix 13 from version 1.0 to frame the following recommendations.

A. Real-World Health Analytics

Regarding Real-World Health Analytics, CDHI recommends adding "Real World Usage" as a new subdomain (a) to collect key performance indicators for assessing real-world usage and re-evaluating the initial SaMD risk level categorization and successive iterations in light of real-world usage and performance data, and (b) to collect data on who are the primary real-world users, both intended and unintended. Do real-world usage and performance confirm or alter the SaMD risk categorization (pp. 25-30)? Is there "off-label" usage or users of the SaMD in the real world? This subdomain has implications for product, organization, and Program performance.

We note that the Program will collect real-world data in ways that permit both initial assessment of aspects of Precertified companies' SaMD (see comments below about interoperability and universal design for examples), as well as longitudinal data needed to understand the evolution of SaMD products over time. Version 0.2's prior shift to real-world performance *analytics* and trends serves this objective, but the key performance indicators must be chosen intentionally to capture initial or short-term performance and longitudinal performance as appropriate.

We also suggest below that the "Human Factor and Usability Engineering" subdomain instead belongs under the "User Experience Analytics" domain.

B. User Experience Analytics

CDHI recommends adding "Workflow" as a separate subdomain, reflecting how important integration with respective clinical, EHR, and other workflows is to users in the real world. Workflow should incorporate the subset of "Implementation" as well, to collect key performance indicators about the initial implementation or installation and integration of the SaMD. These subdomains could be incorporated separately or could be expansions of the "User Engagement" subdomain into a "User Engagement and Workflow" subdomain.

CDHI also recommends adding "Universal Design" as a new subdomain. The framework cannot and does not assume a homogeneous or average user. Developers

must design and build for the diversity of uses and users, and avoid disparities in care and outcomes. Even if we cannot yet build and meet all needs now, we must still anticipate and consider that diversity of uses and users so we do not inadvertently build in significant barriers now to future uses in future iterations. This is the simple principle of universal design. Universal design anticipates and accommodates, for example, the necessary granularity of demographic data such as race, ethnicity, sexual orientation, gender identity, language, and functional and cognitive status needed for competent care, effective clinical decision support, and avoiding or identifying health disparities. This subdomain could be included separately or could be an expansion of the "Human Factors and Usability Engineering" subdomain into a "Human Factors, Usability Engineering, and Universal Design" subdomain.

We suggest that the "Human Factor and Usability Engineering" subdomain instead belongs under the "User Experience Analytics" domain. This subdomain's focus on user comprehension and user interface suggests that User Experience is the more appropriate domain. We also suggest below that the "Issue Resolution" subdomain instead belongs under the "Product Performance Analytics" domain.

C. Product Performance Analytics

Reflecting its national priority under the 21st Century Cures Act, CDHI recommends adding "Interoperability" as a new subdomain, to assess how well the SaMD integrates with open APIs to ensure interoperability without special effort by diverse users. This should include analytics on who is (or is not) actually getting the output needed from the SaMD (e.g. clinicians, patients, etc.). The 21st Century Cures Act addressed the FDA's responsibilities to improve medical device innovation.[2] Congress also declared "interoperability" a national priority and imperative, to assure electronic access, exchange, and use of health information, nationally and locally.[3] Without interoperability, other principles become moot in a digital health ecosystem.[4]

The National Quality Forum's groundbreaking Interoperability Measurement Framework provides excellent examples of interoperability analytics in its Appendix B of measure concepts and existing measures. The Office of the National Coordinator for Health Information Technology (ONC) commissioned the National Quality Forum to develop the Interoperability Measurement Framework, which NQF published in September 2017. It provides the first national framework for measuring the quality, gaps and impact of interoperability across key settings and users of health care. It covers the availability and exchange of electronic health information across the continuum of care, the usability of that exchanged information, its applicability and

[2] 21st Century Cures Act, §§ 3051-3060.
[3] Id., § 4003 (adding 42 U.S.C. § 300jj-12(b)(2)(B)(i), (c)(2)).
[4] 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.

effectiveness, and—the holy grail—the impact of interoperability on health outcomes.[5] The FDA is familiar with this work.[6]

We also suggest that the "Issue Resolution" subdomain instead belongs under the "Product Performance Analytics" domain. The "Issue Resolution" subdomain's use of key performance indicators such as resolution of cybersecurity risks, complaints, and root cause analysis suggests that Product Performance is the more appropriate domain.

With these suggestions, Figure 8 would be (additions in red):

Product Performance Analytics (PPA)	**User Experience Analytics (UXA)**	**Real World Health Analytics (RWHA)**
Cybersecurity	Human Factors, Usability Engineering, and Universal Design	Health Benefits
Product Performance	User Satisfaction	Clinical Safety
Interoperability	User Feedback Channels	Real World Usage
Issue Resolution	User Engagement and Workflow	

The FDA notes that it assesses performance at the product, organization, and Program levels. Figure 8 and Appendix 13 seem structured mostly around product performance, although they include useful metrics for organizational and Program performance, too. The FDA could add three columns to Appendix 13 to show which performance level(s) – product, organization, and Program – the value and KPIs help to measure.

D. Collecting and Reporting Real-World Performance Analytics

The Working Model describes several critical points where the Program will evaluate an organization's and product's capabilities to collect and publish real-world performance analytics.

> During the Excellence Appraisal, all organizations would demonstrate the capability to collect and analyze post-launch RWP data, whether by instrumenting their SaMD products to generate needed data, or by leveraging alternative data sources. (P. 37.)

Not only will the FDA review the capability to collect real-world performance data during the Excellence Appraisal, but it may also evaluate this capability as part of the organization's overall SaMD development process (pp. 32-33) and RWPA plan (pp. 40-41).

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[5] National Quality Forum, *A Measurement Framework to Assess Nationwide Progress Related to Interoperable Health Information Exchange to Support the National Quality Strategy* (Sept. 1, 2017) (report funded by the Department of Health and Human Services), available at https://www.qualityforum.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=85827.

[6] Id. p. 60 (responding to FDA comments).

Instrumenting SaMD and using alternative data sources are not mutually exclusive. All SaMD should be instrumented to collect and report real-world performance data and analytics automatically at the actual point of performance. That is the most efficient approach—instrumenting the SaMD itself to collect and report the data rather than require multiple purchasers and stakeholders each to build separate external systems to measure performance of the same SaMD. For those who elect the Precertification Program and the opportunity to defer assessment to post-market surveillance, instrumenting should be necessary, not voluntary. Instrumenting should be a floor, the minimum to demonstrate capability to "consistently collect and analyze post-launch data related to the safety, effectiveness, and performance of the" SaMD "in order to inform their decision-making related to product or process improvements" (p. 37).

To the extent that an organization's RWPA plan does augment instrumentation data with additional data sources, the additional data could and should include data contributed or managed by the vendor's customers and SaMD users, not just data from the vendor. Such data may include private payer data, data from electronic health records, national databases such as National Evaluation System for Health Technology (NEST) or Medicare, or registries. Where the SaMD is patient-facing, patients may have data to contribute, and likewise they should have full access to their clinical data.[7]

Lastly, the real-world performance data above, while perhaps complete from the product's or vendor's perspective, are still limited, and we encourage the FDA to continue engaging with broader stakeholders to aim for a broader data set that reflects real-world performance including health system implementation, delivery, and experiences with each vendor.

III. TRANSPARENCY IS CRITICAL—TRANSPARENCY ABOUT SAMD COMPONENTS, TRANSPARENCY ABOUT REAL-WORLD PERFORMANCE, TRANSPARENCY ABOUT INTEROPERABILITY

CDHI iterates our recommendation in our prior comment letters, dated May 31 and July 19, 2018, 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, 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.

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[7] We agree with the FDA's suggestion (p. 38) that pre-certified organizations with higher-risk products might also seek external sources of safety and effectiveness data, such as participation in registries, partnerships with healthcare systems, or utilizing data commons or other structured post-market data collection, to supplement instrumented data. Likewise, we agree with the FDA's suggestion (p. 24) that accredited third parties—collaborative communities—could help appraise an organization's culture of quality and excellence, to be used as information in FDA's decision-making. Measurement by accredited third parties in actual SaMD environments such as health systems, consumers, payers, comes closer to measuring real-world experience and performance, not just laboratory measurement. It can also help provide independent validation of the PreCert program itself and the FDA's measurements in a regulatory environment.

At a minimum, all stakeholders—from developers to users to regulators—need to know what is inside. This is akin to the traditional software bill of materials, which lists the software's components, including open-source and third-party software components.[8]

Secondly, in the absence of the usual pre-market clinical trials to demonstrate efficacy before approval, post-market surveillance and disclosure of real-world performance data are essential. The FDA already requires standardized drug labelling for therapeutics. Similar, standardized transparency and disclosure should be required for digital therapeutics such as SaMD. Users need and deserve a complete summary of results, not one that might have been "cherry-picked" to exclude data that a vendor might otherwise prefer to suppress, such as adverse results, unexpected results, unintended results, or off-label uses. For example, transparency and disclosure should include the real-world performance analytics collected in Appendix 13. Indeed, transparency and complete disclosure of real-world performance analytics should contribute significantly to increasing organizational excellence, which is a core value of the Program.

We recognize that there can be different levels of transparency. Just as the FDA wants analytics and trends, not the raw data, transparency to users does not require disclosure of an organization's raw data. But an accurate summary and analytics are critical.

Third, to ensure interoperability, SaMD should also use and integrate with open APIs. ONC's 2015 Edition criteria for certified EHR technology and health IT require open APIs and specify the minimum public documentation required to ensure access and ability to innovate and integrate other applications that improve usability and care.[9]

Such summaries and transparency are what academic medical centers such as UCSF would typically expect as part of any internal decision and quality control to implement and use—or not—particular software as a medical device. A successful Precertification Program should integrate that open documentation and transparency for better health and care across the nation.

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[8] The FDA is already promoting a software bill of materials in its Medical Device Safety Action Plan, issued April 2018, "that must be provided to FDA as part of a premarket submission and made available to medical device customers and users, so that they can better manage their networked assets and be aware of which devices in their inventory or use may be subject to vulnerabilities. In addition, availability of a 'Software Bill of Materials' will enable streamlining of timely postmarket mitigations." FDA, Medical Device Safety Action Plan: Protecting Patients, Promoting Public Health, p. 13 (Apr. 2018), available at https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM604690.pdf.

[9] 45 CFR § 170.315(g)(9)(ii); see also 80 Federal Register 62602, 62679, 62754-62755 (Oct. 16, 2015). For example, the 2015 Edition requires accompanying public documentation that includes, at a minimum:

> (A)(1) API syntax, function names, required and optional parameters and their data types, return variables and their types/structures, exceptions and exception handling methods and their returns.
> (2) The software components and configurations that would be necessary for an application to implement in order to be able to successfully interact with the API and process its response(s).
> (3) *Terms of use.* The terms of use for the API must be provided, including, at a minimum, any associated developer policies and required developer agreements.
> (B) The documentation used to meet paragraph (g)(9)(ii)(A) of this section must be available via a publicly accessible hyperlink.

IV. A NOTE ABOUT WHO ARE THE STAKEHOLDERS

Lastly, version 0.2 refers at various points to "all stakeholders" in the Precertification Program. Appendix 13 identifies the importance of each subdomain to "all stakeholders," and Table 1 appears to list those stakeholders. We suggest a few additions to ensure that they are not overlooked.

First, payors include insurers, but also include employers and other purchasers.

Second, vendors are not just the SaMD developers, but include other developers as well such as EHR developers that integrate the results.

Lastly, we suggest that researchers are an important stakeholder group, for they are often important on the front end in developing the algorithms, and are important throughout in the process of iteration.

Conclusion

Thank you for the opportunity to provide these comments on version 1.0 of the draft Working Model. In general, we think that the Working Model continues to be 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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