

FDA-2018-N-1910

**VIA ELECTRONIC SUBMISSION**

June 21, 2018

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

**Re: Docket No. FDA-2018-N-1910: Development of 21st Century Cures Act  
Section 3060 Required Report: Request for Input**

Dear Sir or Madam:

On May 29, 2018, FDA requested input on the benefits and risks to health associated with the medical software functions excluded from the device definition (under section 201(h) of the Food, Drug, & Cosmetic Act (“FDCA”) by the 21st Century Cures Act (“Cures Act”). More specifically, with regard to the five enumerated categories of non-device software functions, which include software intended to provide clinical decision support (“CDS”), FDA expressed interest in gathering information related to “patient safety, including best practices to promote safety, education, and competency related to such functions.”

In response to this request, the Clinical Decision Support Coalition (“CDS Coalition” or the “Coalition”) would like to offer information on:

1. The benefits of CDS software; and
2. Industry’s efforts to develop and implement guidelines that identify appropriate disclosures designed to promote “safety, education and competency” related to CDS software unregulated by FDA.

**I. Background on the Coalition**

By way of background, the CDS Coalition is a diverse group of stakeholders consisting of software providers, IT infrastructure manufacturers, healthcare providers, medical device and pharmaceutical manufacturers, trade groups and members of the clinical community. Focused on clinical decision support software, the Coalition’s goal is to ensure a risk-based and clearly defined regulatory system for such software that appropriately balances the need for regulatory oversight with the need for innovation and access to new technology.

## II. Benefits of CDS Software

CDS software covers a very broad range of software that is designed, at least in part, to help practitioners avoid common mental errors. Errors by healthcare professionals are a considerable source of morbidity and mortality in the United States. In fact, researchers estimate that medical errors account for over 250,000 deaths per year in the United States, making it the third leading cause of death.<sup>1</sup> The benefits of CDS software seem reasonably well-established in the literature. As we assume that the Agency has, or will, appropriately canvass the literature in compiling the list of benefits of CDS software, we will not attempt to summarize the relevant literature here.

Instead, we simply want to remind the Agency of the benefits of CDS software in one particular realm that we have previously addressed. On August 16, 2016, the Coalition filed a citizen petition requesting that the Agency clarify its regulatory approach with regard to CDS software used in tandem with pharmaceutical products. In that petition, we laid out the benefits of combining pharmaceuticals with digital health products, and we reproduce them here as Appendix A. We note that we are coming up on two years since the filing of that petition, and to our knowledge, the Agency has yet to produce a response.

## III. Industry CDS Guidelines

Beyond our August 2016 citizen petition, in 2017, the CDS Coalition went through a rather substantial public process to develop consensus guidelines for unregulated, medium and low risk CDS software. The document developed, entitled “Voluntary Industry Guidelines for the Design of Medium Risk Clinical Decision Support Software to Assure the Central Role of Healthcare Professionals in Clinical Decision-Making,” together with an introductory memorandum, are attached as Appendix B. Below, we describe how the guidelines were developed and discuss the purpose we intend them to serve.

### A. Development Process

In developing the consensus guidelines, we solicited comments from interested stakeholders as well as the Agency. To publicize our interest in receiving comments, we posted the draft guidelines on our website, and prepared a summary of the guidelines that we posted as an article on LinkedIn. Members of the Coalition made significant efforts to publicize the availability of the draft for comment, sharing the article with their LinkedIn networks. During the commenting period, which was open for 60 days, 750 people read the summary article on LinkedIn and 95 people chose to share the article with their networks.

In addition to the public comment phase, we solicited comments from FDA. Specifically, we met with FDA’s Digital Health Task Force to present these guidelines. During that meeting, we received useful suggestions from the Agency about how we could improve the guidelines.

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<sup>1</sup> Martin Makary & Michael Daniel, *Medical Error – The Third Leading Cause of Death in the US*, 353 *BMJ* i2139 (2016), available at <http://www.natap.org/2016/AGE/bmj.i2139.full.pdf>.

In the end, we produced not only the guidelines, but an introductory memorandum in which we recited the various comments we received, and our responses, much like the preamble to a final rule. We felt as though providing that statement of purpose was important context to interpreting the guidelines.

B. Guidelines Produced

Over the last several years, many companies developing CDS software have been sorting through the various design options for empowering the user to take control of the decision-making. In this quest, some companies have been looking for guidelines on the proper approach to user engagement. Further, many companies are exploring the use of machine learning and other forms of artificial intelligence to power CDS software. But the adoption of those technologies brings with it the challenge of keeping the user in control of the decision-making.

That is where the Coalition's industry guidelines come in. For CDS software that FDA does not regulate, industry is best served by self-regulating through the adoption of basic software design guidelines. To that end, these guidelines are intended to foster the design of software in such a manner that healthcare professional users will be able to independently review the basis for the recommendations the CDS software produces, such that the professionals will not need to rely primarily on the recommendations. The purpose of these guidelines is to provide a unified approach that CDS software developers can employ to ensure they are providing at least a basic level of transparency and the opportunity to review the basis of the recommendations made.

At their core, these guidelines are intended to give software developers a framework for discerning whether additional validation – beyond that which they would ordinarily do – is required as a consequence of the software taking over decision-making from healthcare professionals. These guidelines reflect the view that taking over, in any substantial way, the healthcare decision-making carries with it heightened responsibility for validation.

We believe that the existence of these guidelines is directly relevant to FDA's question about efforts to promote safety, education, and competency related to CDS software. We believe that they stand as evidence that industry is making appropriate efforts to self-regulate in this space, and that FDA oversight of medium and low risk software is not necessary. Indeed, FDA regulation of medium and low risk CDS software threatens to stifle innovation in a very important technological space.

Please let us know if you have any questions or need any further information.

Yours truly,

A handwritten signature in black ink, appearing to read "Bradley Merrill Thompson". The signature is fluid and cursive, written over a light gray horizontal line.

Bradley Merrill Thompson  
General Counsel, CDS Coalition

## **Appendix A: Excerpt from the CDS Coalition’s August 2016 Citizen Petition**

### *1. Importance of Digital Health Technology Innovations and Trends*

#### a. The Therapeutic Benefits of Combining Pharmaceuticals with Digital Health Products

In his 2012 book, *The Creative Destruction of Medicine: How the Digital Revolution Will Create Better Health Care*, Dr. Eric Topol outlines the changes he foresees in the life sciences industry. Focusing on the future of pharmaceuticals, he offers an example of what he foresees as follows:

Combining genomics and digital imaging, along with sensors that detect cognitive ability on a frequent or continuous basis – the sort of thing one could program to run on a smart phone – could collectively be used to identify a drug intervention with particular promise and precision for preventing or markedly delaying the onset of Alzheimer’s. ... The third limb of this digitized approach is confirmation or titration of the desired effects with the use of wireless sensors. We don’t even have a word for that yet, but the triad package of some type of biomarker, a therapy, and a wireless sensor would be an exceptionally powerful means for catapulting medicine into the future.

That was four years ago, and the future is now. Researchers all over the world in universities, pharmaceutical companies, technology companies and provider systems are exploring the combination of digital health technologies with pharmaceuticals to achieve not just greater adherence, but better care.

Some of these joint initiatives between pharmaceutical companies and tech companies have been publicly reported. However, those in the public domain represent only the tip of the iceberg. The vast majority of this research is proprietary, and is being done behind closed doors. But the members of the CDS Coalition can attest that this area of combined pharmaceuticals and digital health products is an area of major focus in research, and frankly, the cause for great optimism.

There are several factors driving the combination of pharmaceuticals and digital health products. Those drivers include:

- advancements in wearable sensor technology that allow sensing and electronically sharing a huge array of body signals of relevance to the treatment of patients;
- the evolution of the Healthcare Internet of Things, which allows for the stitching together of many different electronic constituent parts to allow for a more unified assessment of patient status and monitoring;
- advancements in medicine that allow us to understand the progression of disease, such that we know which body indicators and biomarkers to watch, as well as advances that help us understand the very personalized response of the body to medication; and
- advancements in pharmaceutical care that provide a better understanding of how disease progression can be studied and used to more effectively choose the timing and selection of pharmaceutical products.

All of these advancements, taken together, mean that a new model is emerging for treating disease that considers treatment strategies based on systems made up of many components, not just pills in isolation.

This is really the consequence of the elevation of systems thinking into mainstream healthcare. This sea of change has progressed to the point where one of the newest medical schools to launch – at University of Illinois in Champaign Urbana – is completely upending the traditional medical school curriculum; the school combines medicine and engineering into a single program, with systems thinking throughout in order to train a new breed of physician.<sup>2</sup>

#### b. Three Case Studies

The members of the Coalition worked together to develop three case studies that collectively embody the issues that the industry is consistently facing in developing CDS products. These case studies involve products that show great promise in the future of pharmaceutical care, with each designed to address a critical clinical need.

##### i. Adherence Enhancing Digital Health Products

In a nutshell, here's the problem:

Medications are the primary tools used to prevent and effectively manage chronic illness; however, despite their importance and known benefit, appropriate medication use remains a challenge for both patients and providers. Patients frequently do not adhere to essential medications, resulting in poor clinical outcomes, increased cost of care, and deleterious consequences for workforce productivity and overall public health. Half of the 3.2 billion annual prescriptions dispensed in the United States are not taken as prescribed. Numerous studies have shown that patients with chronic conditions adhere only to 50-60% of medications as prescribed despite evidence that medical therapy prevents death and improves quality of life.

Estimates are that approximately 125,000 deaths per year in the United States are due to medication non-adherence and between 33 and 69 percent of medication-related hospital admissions in the U.S. are due to poor adherence. While some of the relationship between poor adherence and poor outcome is due to confounding factors, the lost opportunity for effective therapies to improve health is staggering. For example, cardiovascular medications alone are estimated to be responsible for half of the 50% reduction in mortality from coronary heart disease over the past 20 years. Yet actual achievement of these cardiovascular benefits is lost due to high rates of non-adherence in real-world settings. In fact, the true rate of non-

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<sup>2</sup> Carle Illinois College of Medicine, <https://medicine.illinois.edu/> (last accessed June 22, 2016).

adherence may be higher as patients with a history of non-adherence are likely underrepresented in trials outcomes research.<sup>3</sup>

To address the problem of non-adherence, pharmaceutical companies are partnering with digital health product developers to create a suite of products that can be packaged around pharmaceutical use to encourage greater adherence. One of the strategies for motivating greater adherence is to create a stronger connection between taking the medicine and seeing healthcare improvement. The second case study squarely addresses the issue of software and wearables woven together to help the patient see more directly the benefits of taking medicine as prescribed, with an aim toward enhancing compliance.

## ii. Disease Management Digital Health Products

The drive toward personalized medicine is well known. Indeed, the U.S. Food and Drug Administration (“FDA” or the “Agency”) itself describes the goals quite aptly in its October 2013 report on *Paving the Way for Personalized Medicine: FDA’s Role in a New Era of Medical Product Development*:

The concept of personalized medicine is not new: The practice of medicine has always been about treating each individual patient, and clinicians have long observed that different patients respond differently to medical interventions. What is new is that paradigmatic developments in science and technology offer new promise for developing targeted therapeutics and tools for predicting who will respond to a medical therapy or who will suffer ill effects.<sup>4</sup>

Indeed, in this report, FDA shares a number of steps it is taking to clarify the pathway to market for products that seek to embody the benefits of personalized medicine. Specifically, FDA focuses squarely on the need to clarify regulatory authorities for different products used together to achieve personalization. FDA observes:

Personalized medicine generally involves the use of two or more medical products, such as a diagnostic test to determine whether a patient may or may not benefit from a particular therapeutic intervention, and the therapeutic product itself. Often, these products are: (1) regulated under different regulatory authorities (e.g., drugs vs. devices); (2) regulated by different FDA Centers (e.g., CDER vs. CDRH); and (3) owned and manufactured by different companies.<sup>5</sup>

FDA describes the conundrum of digital health products used with pharmaceuticals to a tee, but then seems to focus exclusively on companion diagnostics – which are extremely important –

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<sup>3</sup> Hayden B. Bosworth, et al., *Medication Adherence: A Call for Action*, 162 *Amer. Heart J.* 412 (2011), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3947508/>.

<sup>4</sup> U.S. Food & Drug Admin., *Paving the Way for Personalized Medicine: FDA’s Role in a New Era of Medical Product Development* 4 (2013), <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PrecisionMedicine/UCM372421.pdf>.

<sup>5</sup> *Id.* at 32.

and does nothing to identify a course of action for clarifying the pathway to market for this particular combination of products.

We need clarity for digital health products as well. The first and second case studies present these issues very concretely.

### iii. Clinical Guideline Interpretation Products

We have long known that practicing physicians can be overwhelmed by the enormous and growing body of medical evidence that we ideally want them to understand and incorporate into their practice.<sup>6</sup> In the U.S. alone, it is estimated that up to 20 percent of diagnoses are either incorrect or incomplete.<sup>7</sup> In addition, there are an estimated 1.5 million errors in the way medications are prescribed, delivered and taken in the U.S. every year. These mistakes could be greatly reduced if doctors had access to the latest relevant medical information. But there is so much medical data in the world that it is impossible to keep track of it all. Medical information is doubling every five years. Although the volume of information is rapidly increasing, we are entering an era where computers can help practicing physicians sort through all of the information they need to manage in order to arrive at the best possible decision.<sup>8</sup>

The third case study takes on a relatively simple aspect of this new wave of clinical decision support software aimed at helping doctors understand and apply clinical guidelines. In prescribing medication, doctors routinely need to correctly apply clinical guidelines to help them judge the need for treatment. Some clinical decision software in this area involves a rather simple and straightforward embodiment of a singular clinical guideline. But as we progress, the desire is to become more sophisticated in applying the broader body of clinical knowledge to physician decision-making. As we move in that direction, the FDA issues get more complicated. The third case study reflects a common scenario facing pharmaceutical care today.

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<sup>6</sup> See Richard Smith, *Information in Practice*, 313 *BMJ* 1062 (1996). <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2352351/pdf/bmj00565-0044.pdf>; Rachel Chan & Vivian Stieda, *Evaluation of Three Point-of-Care Healthcare Databases: BMJ Point-of-Care, Clin-eGuide and Nursing Reference Centre*, 28 *Health Information & Libraries J.* 50 (2011), <http://www.ncbi.nlm.nih.gov/pubmed/21314894>; Eta S. Berner & Jacqueline Moss, *Informatics Challenges for the Impending Patient Information Explosion*, 12 *J. Amer. Med. Information Assoc.* 614 (2005), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1294032/>.

<sup>7</sup> IBM Research, *The Doctors Are In*, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4287097/> (last accessed June 22, 2016).

<sup>8</sup> *Id.*

## Introductory Memorandum

To: Those interested in the Voluntary Industry Guidelines for the Design of Medium Risk Clinical Decision Support Software to Assure the Central Role of Healthcare Professionals in Clinical Decision-Making

From: CDS Coalition

Date: August 30, 2017

Re: Coalition's Reactions to Public Comments on the Voluntary Industry Guidelines

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### **I. Overview**

The Coalition would like to thank all those who took the time to submit comments on our draft guidelines earlier this summer. We received many comments, and it is obvious to us that quite a few people took the time to patiently study the guidelines, and offer terrific suggestions.

Although the Coalition's membership is broad and diverse – spanning from health information technology developers and medical device and pharma companies to nonprofit healthcare associations, providers, healthcare professionals, payers and patients (representing more than 40 institutions altogether) – we recognize that many other stakeholders are interested. So we set out to collect input from everyone interested in this project.

To publicize our interest in receiving comments, we posted the draft guidelines on our website, and prepared a summary of the guidelines that we posted as an article on LinkedIn. Members of the Coalition made significant efforts to publicize the availability of the draft for comment, sharing the article with their LinkedIn networks. During the commenting period, which was open for 60 days, 750 people read the summary article on LinkedIn and 95 people chose to share the article with their networks.

In addition to the public comment phase, we solicited comments from FDA. Specifically, we met with FDA's Digital Health Task Force to present these guidelines. During that meeting, we received useful suggestions from the Agency about how we could improve the guidelines.

### **II. Summary of Public Comments Received**

Through the comments, we received almost unanimous support for the basic principle that enabling a healthcare professional to independently review the basis for recommendations the software makes requires transparency by the software, competent human intervention and time to



reflect. Those are the three pillars of the guidelines, and there seems to be ample agreement on that front.

We did, at the same time, receive several comments with helpful suggestions to improve how those three goals are achieved. We have made changes throughout the guidelines to address important comments that members of the public submitted. This public input has been invaluable and we truly believe that it has significantly improved the guidelines.

Based on stakeholder comments, we have made certain changes to the text of the guidelines. However, we think some of the comments merit a more fulsome discussion. This memorandum provides that discussion, including the Coalition's responses to such comments, which we hope will provide greater insight into our thinking and intentions. Therefore, this introductory memorandum will form a sort of permanent explanation for the purpose behind some of the guidelines' elements. Much like a federal agency does when responding to comments on a rule, this memorandum could be considered the preamble to the guidelines.

Below we summarize some of the major comments received, and explain how we address them.

A. Too prescriptive

**Comment:** Several commenters thought the guidelines were too prescriptive, in effect demanding one approach, and one approach only, to assuring that the healthcare professional remains in control. These commenters observed that there is likely more than one way to assure that result, especially given the wide variety of approaches to developing software in this space.

**Response:** We agree, and we revised the guidelines to emphasize that the approach outlined below is simply one approach, and that developers should feel free to develop other approaches that they can justify as equivalent in accomplishing the purpose of keeping healthcare professionals in control of the decision-making. We included a fair amount of detail because we thought the detail would be helpful in understanding the approach that we were suggesting, but we absolutely understand that this is only one approach and that others are likely to be satisfactory. We would simply urge the companies that want to take a different approach than the one outlined in these guidelines to memorialize in their own design files the justification for taking a different approach, and why it produces an equivalent result.

In memorializing the differences between a developer's particular approach and what these guidelines recommend, we think it is important that software developers conduct usability testing on their software to ensure that the overall objective of these guidelines is met. That objective is leaving the healthcare professional fully in control of the decision-making such that he or she has a reasonable opportunity to independently review the basis of the recommendation. The software developers will need to create testing protocols that evaluate their particular software in their particular use cases to ensure that objective is met.

B. Too complex

**Comment:** A few commenters felt the guidelines are too complex.

**Response:** The guidelines are complex, and we recognize that simplicity is a virtue. The challenge, to us, is that this topic is very complex in and of itself, and it is made even more complex by the fact that there is great variety in the ways that software is developed in this space and each requires its own approach.

We have tried to address the complexity by providing an overview on pages 15 through 18 that lays out the general principles at a high level. Frankly, if a reader stops there, the reader would have a good understanding of the general approach. The appendices do provide detail to cover the myriad of different software packages, but most readers could take the overview and apply it effectively without even reading the appendices. The overview is the simple approach, expressing certain simple truths.

### C. Need for “design guidance”

**Comment:** One comment asked the rhetorical question of why industry needs design guidance in this space.

**Response:** As a result of the 21<sup>st</sup> Century Cures Act, certain CDS software will not be regulated by FDA. The exact line drawn by the statute will need to be interpreted by FDA, and we want to give FDA confidence that for that software the Agency does not regulate, industry will do an adequate job of self-regulation. The legislation provides an avenue for FDA to clawback into regulated territory any software that the Agency finds may lead to serious injury or death in patients. If industry does an adequate job of self-regulating and therefore avoiding such patient injury, industry can reduce the likelihood that FDA will need to expand the scope of its regulation.

At a high level, the impact of the design guidelines is to discern when additional software validation is required, beyond the normal baseline, because the software will be taking over certain clinical decision-making from the healthcare professional. In other words, a purpose of the guidelines is to make sure that companies are very deliberate and thoughtful about when they cross the line to take over decision-making from the healthcare professional. Such a line should not be crossed casually, nor should it be crossed without giving thought to the additional validation such a step may require.

In the experience of some of the members of the Coalition, feedback collected from healthcare professionals during initial market research as well as user testing is terrific at collecting helpful input on the software’s usefulness, ease of use and simplicity, clarity and speed. But this testing and feedback does not always address the issue of whether the user remains fully in control of the decision-making. Thus, these guidelines are intended to bring a deliberateness to the developer’s thought process regarding the issue of whether the developer wants to take the steps necessary to ensure the user remains fully in control, or whether the software developer decides that it’s better to take over some of the decision-making and correspondingly increase the level of validation the software may need.

The bottom line is that we think these design guidelines are needed to bring focus and attention to design decisions around whether, and if so how, to leave the healthcare professional in control of the decision-making.

D. Exceeds the legal minimum

**Comment:** At least one commenter thought that the guidelines exceed what the 21<sup>st</sup> Century Cures Act would require.

**Response:** That commenter may well be right. But identifying the legal minimum under that statute was never the goal of the Coalition. That issue will be up to the FDA as the Agency interprets the 21<sup>st</sup> Century Cures Act.

This exercise was not done by asking lawyers to sit in a conference room together to hash out what they thought the statute minimally required. Instead, the Coalition – which is comprised of people who are developing and using such software – looked to identify, practically speaking, what the minimum should be for ensuring that the healthcare professional remains in control.

We would also add that there is much more to be considered than just the 21<sup>st</sup> Century Cures Act. In this area, both product liability and medical malpractice, as well as the regulatory oversight of the practice of medicine, all speak directly to this issue and must be considered.

E. FDA is expanding the unregulated category

**Comment:** Over the course of the summer of 2017, new FDA Commissioner Gottlieb has made a few announcements regarding anticipated changes in the Agency’s approach to regulating software generally, including MR-CDS. Among other things, he suggests that the Agency may go beyond what the statute requires, and exempt a few other categories of software.<sup>1</sup> Furthermore, FDA has announced a pilot program that will begin this fall intended to examine fundamentally different approaches to regulating software.

**Response:** We live in exciting times, and we share the optimism that FDA will one day make substantial changes in its regulatory approach to software. But the policy, legal and regulatory processes being what they are, those changes could still be years off. In the interim, we developed these guidelines for the present state of FDA regulation as defined by the 21<sup>st</sup> Century Cures Act. Should that environment change in important ways relevant to these guidelines, we will work to keep the guidelines up-to-date reflecting the current regulatory approaches.

But please understand those changes may simply make these guidelines more important. Fundamentally, we have identified this space because under the Act, this category of software will not be regulated. Thus, if FDA does indeed expand the scope of what is unregulated, the guidelines will grow in importance.

F. Clicks are outdated

**Comment:** Several commenters suggested that the concept of a “click” is on its way out, and that other approaches to navigation such as voice activation may well be used. Others, more

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<sup>1</sup> See Scott Gottlieb, *Fostering Medical Innovation: A Plan for Digital Health Devices*, FDA Voice (June 15, 2017), <https://blogs.fda.gov/fdavoices/index.php/2017/06/fostering-medical-innovation-a-plan-for-digital-health-devices/>.

substantively, suggested that the whole architecture of software may change, making the whole concept of moving from page to page outdated.

**Response:** While we will update these guidelines in the future with regard to new approaches, for now, we simply recommend this as a basic framework to communicate the ease and speed with which users should be able to access certain information. In that sense, at a higher conceptual level, we are simply trying to put into three different levels how immediate the need is for the user to be able to access specific categories of information.

Further, while clicking is an issue of navigation, the essential framework we are using is based on links. Whether internally contained or externally accessible information, we are describing how many links the user should be expected to use to access the information.

In the future, the Coalition is likely to develop a functional test that relates the time and effort needed to delve into the supporting information to the work environment (e.g., more time in a consultative visit, less in the ER). For example, the best interface in some situations may be an AI-empowered voice platform in which the practitioner is having a “conversation” with the AI virtual colleague. We will need to develop a parallel guideline for this type of technology.

#### G. Professional categories are outdated

**Comment:** Several people told us that our vocabulary with regard to professional categories was outdated, and we are not allowing for the relatively fluid nature of health professional regulation that allows emerging categories like nurse practitioners to take on more and more responsibility. Thus, not only was our vocabulary out of date, but we need to account for the somewhat fluid and overlapping nature of the categories.

**Response:** The comment is indeed a good one. We have made changes to the names of the categories to reflect more current nomenclature.

While coming up with specific guidelines in an area that is fluid is difficult, the basic principle here is not. MR-CDS developers should only target users who are competent to make the decision the software would support. It is a deceptively simple point. We chose to put professionals in three buckets because that seems to be a way to convey simply the range of decision-making afforded under the licensing laws. But for those who prefer even greater simplicity, we say, “Don’t through your software try to empower people to make decisions they aren’t otherwise qualified to make.”

**Comment:** One person suggested that we go so far as to suggest ways that software developers can recommend that their customers control who uses their software. For example, the suggestion was made that in labeling, the vendor recommend that user institutions tie the use of the software to credentialing, using that to control access.

**Response:** We think in most cases it will be unnecessary for the software vendor to make specific suggestions to the user institution about how they institution should use their software. So long as the software vendor is clear about the appropriate level of qualifications anticipated for the appropriate user, it should be up to the institution to decide how it actually wants to control the use.

H. Competent human intervention and time to reflect requirements should be risk-based

**Comment:** One comment observed that we had bifurcated the requirements for transparency based on high and low risk, and that it made sense to similarly bifurcate the competent human intervention and time to reflect requirements based on risk.

**Response:** That's a great idea. We should've thought of that, but didn't.

We have gone back through to parse the requirements with regard to competent human intervention and time to reflect to segregate those that should be only applicable to the higher risk devices, and those that frankly ought to be met regardless of risk.

I. The guidelines should incorporate ONC's approach to transparency

**Comment:** Two comments suggested that we consider incorporating the approach to transparency recommended by the Office of the National Coordinator (ONC) of using links.

**Response:** We do indeed believe that links could be a very suitable way to share relevant information needed to assess the basis for a recommendation. But we declined to simply adopt the ONC approach because we believe that approach was adopted for a different, more general purpose. The ONC did not recommend its approach as the pivotal point for deciding whether additional validation might be required, but rather recommended the approach as general good practice.

In these guidelines, we are very specific in articulating the standards that developers should consider when deciding whether additional validation is required. The ONC requirements, while interesting and useful, do not appear to be intended to establish that minimum.

J. What does transparency mean: sharing the math or sharing the validation of the math?

**Comment:** Several comments focused on machine learning. In that context, they argued transparency really doesn't so much mean providing an explanation of how the software arrived at its conclusion, but rather demonstrating that the software has been validated to the point where the user can take comfort that the recommendations are likely correct.

**Response:** To some extent, that comment merges the two alternative pathways to market reflected in the guidelines. What the guidelines say, in effect, is that software developers can avoid extra and expensive validation – beyond what would normally be done – if they avoid taking over the decision-making from the healthcare professional. Extra validation is, in fact, the alternative pathway to market if the software cannot assure that the healthcare professional can independently review the basis of the software's recommendations.

Nevertheless, we do not believe that all machine learning necessarily must follow the extra validation/FDA regulation pathway to market. We believe that there is a pathway through which

enough information can be communicated to the healthcare professional user about the machine learning software that would give the professional that reasonable opportunity to review the basis for the recommendation.

This is an emerging area, and we recognize that many people are studiously working to figure out a way to make machine learning software less of a black box. For example, biomedical research scientists are working to address the challenge of articulating machine learning models in a clear and concise manner.

In the meantime, there are five key steps developers can take:

1. **Explain what can be explained.** Don't make the problem bigger than it has to be. If the software is actually a blend of expert systems and machine learning, and if a particular recommendation is based on expert systems, such as simply looking up the drug allergy in the patient's EHR, following a simple computational model or recommending a treatment because it is cheaper, the recommendation ought to reveal that reason.
2. **Communicate the quality of the machine learning algorithms.** When the source is truly machine learning, the software needs to reveal that source, along with information that will help the user gauge the quality and reliability of the machine learning algorithm. Through a page in the user interface that can be periodically updated, the developer could explain to the user the extent to which the system has been validated and the historical batting average of the software. That context helps the user understand the reliability of the software in general.
3. **Describe the data sources used for learning.** Providing a thorough explanation of the data sets used to feed and test the machine can provide important context and assurance to the clinician.
4. **State the association as precisely as possible.** With machine learning, really what we are seeing is an association — something in the patient-specific information triggers an association to what the software has seen in other cases. Even though the software can't articulate exactly what it is about the data that triggers the association or even what features it looked at, that doesn't make it any different than a radiologist who points to a place on an image and says, "I've seen that before, and it's been malignant." Much of what we "know" in medicine is really just associations without a deeper understanding of a causal relationship. Software built on machine learning needs to explain that it has spotted an association, and state as precisely as it can the details of that association.
5. **Convey the confidence level.** While software based on machine learning does a miserable job of explaining the clinical logic it follows, machine learning excels at communicating its confidence level in reaching a particular recommendation. And that's quite valuable. That information helps the user decide how much deference the user should give a particular recommendation.

Some argue that in the future, we won't need to rely as much upon individual physicians at the point of care, but rather we should use committees of experts to rigorously review and approve

software for use. Since that approach is not spelled out in the 21<sup>st</sup> Century Cures Act, we have not tried to address it here.

K. Broadening the scope of MR-CDS

**Comment:** Several organizations observed that some MR-CDS is not focused on one singular disease and therefore does not simply provide one singular recommendation. They observed that some software provides multiple recommendations that are not alternatives to each other, but instead address various comorbidities.

**Response:** We agree with that comment, and have revised the definition to include software that recommends more than one diagnostic decision and/or therapeutic recommendation, so long as they are not alternatives to each other, but rather complementary to each other.

**Comment:** Some organizations, in their comments, wanted to expand the scope of these guidelines to include software that produces a range of possible recommendations. They seemed concerned that such software would not be within scope for two separate reasons. First, some observed that the vernacular term CDS was understood to be broader than the scope of these guidelines. Second, others commented that software that does nothing more than narrow the universe of possible solutions from nearly infinite to say 10 possibilities carries risk, because the software might inappropriately exclude possibilities that the healthcare professional should consider. In a sense, they were expressing a concern for something akin to the risk of false negatives. If the best answer is not found among the search results, then the search results are steering the user down the wrong path.

**Response:** Of those two comments, the first is the easier to address. The fact that we are defining CDS for purposes of these guidelines narrower than the vernacular meaning seemed to be causing confusion. At the same time, because the task of developing these guidelines is not to focus on vernacular definitions, but to focus on the software that presents enough risk to merit being subject to these guidelines, we addressed this comment in our revisions by inventing our own term to describe the narrower set of CDS on which these guidelines would fall.

As we explain in the revised guidelines, FDA will regulate high risk CDS software where, among other things, (1) the user does not have a reasonable opportunity to review the basis of a recommendation and (2) the software performs important functions where, should the software not work as intended, someone could get seriously hurt. Further, in our judgment, low risk CDS software where the risk of injury is low regardless of whether there is reasonable opportunity to review the basis for the recommendation need not be burdened by these guidelines. Instead, these guidelines focus on what we call “medium risk clinical decision support” software or “MR-CDS,” which naturally enough falls between those two other categories.

The comment about risk is harder to address. There is, though, a fundamental principle involved here: **Effective involvement by healthcare professionals mitigates risk.** Indeed these guidelines are based on the fundamental principle that enabling healthcare professionals to remain fundamentally in control of the decision-making substantially reduces the risk. In other words, these guidelines aim to reduce risk by ensuring that the healthcare professional can effectively review the basis for recommendations. And that is very important for MR-CDS.

The corollary that helps to define low risk CDS is software in which the user must remain actively, mentally engaged. Software that produces a range of possible options – without singling out one or multiple recommendations that should be followed-- is lower risk for the simple reason that it forces the health care professional to remain actively, mentally engaged. By not producing a crisp recommendation, the software forces the physician or other healthcare professional to sort through the range of options and to think about what the right answer may be.

That is why we choose to limit the scope of these guidelines to MR-CDS, and to exclude low risk CDS. The burden of these guidelines is simply not justified for low risk CDS. To be clear, vendors of low risk CDS still need to be responsible, and are still held accountable to certain standards by product liability laws and other similar legal requirements. So a basic level of validation is still required even for low risk CDS. And indeed vendors of low risk CDS should consider at least portions of these guidelines to the extent they reflect best practices. But these guidelines do not require vendors of low risk CDS to do so.

**Comment:** Other commenters wanted us to make it clear that when software presents alternatives, but they are communicated in probabilistic terms, so that the reader has a clear understanding of which are the most likely, such software would qualify as MR-CDS that is subject to these guidelines.

**Response:** We agree, and we are revising the definition of MR-CDS to make clear that software that produces such probabilistic recommendations is subject to these guidelines.

#### L. Clarifying the role of labeling

**Comment:** Several commenters pointed out that the word labeling is a little bit confusing. Software doesn't have what people would normally call labeling per se. Commenters point out that there is a big difference between purchasers and users, in that much software is purchased institutionally and then used by healthcare professionals individually.

**Response:** We have endeavored to clarify the difference between information that we think should be communicated to a purchaser during the promotion of the software, and information that we think should be communicated to users integrated into the workflow. The former we call promotional labeling, and the latter we call instructions for use. In the chart below, we summarize which requirements should be applicable in which instances.



Promotional Materials to Buyer	Instructions for Use Embedded in the Software for User
<ul style="list-style-type: none"> <li>▪ Limits of software’s functionalities <ul style="list-style-type: none"> <li>○ Indications for use</li> <li>○ Contraindications</li> </ul> </li> <li>▪ Necessary qualifications of the intended user</li> <li>▪ Environment in which the software is intended to be used</li> <li>▪ Whatever amount of time is needed to appropriately use, and double check the recommendations of, the software</li> <li>▪ Information outside the software the user may wish to consider</li> </ul>	<ul style="list-style-type: none"> <li>▪ Limits of software’s functionalities <ul style="list-style-type: none"> <li>○ Indications for use</li> <li>○ Contraindications</li> </ul> </li> <li>▪ Necessary qualifications of the intended user</li> <li>▪ Information outside the software the user may wish to consider</li> </ul>

M. Accessibility of the underlying clinical guidelines

**Comment:** During the comment process, we received a question about what exactly the term “reasonably accessible” means in Appendix A, Table 2.b.ii.2.B. Among other things, the commenter expressed concern that some materials are subject to copyright.

**Response:** In these guidelines, we declined to elaborate on what that term means because there are too many variations of how a company might make the information accessible. As with any other element of these guidelines, if a company cannot achieve reasonable access for the user, the company has the option of additional validation and potentially subjecting the software to FDA regulation, since the output must be accepted more on faith than fact. We would encourage developers to appreciate the purpose of this requirement – leaving the healthcare professionals in control of the decision-making – and to identify creative ways of accomplishing that. We recognize that in some cases these options may also be expensive, but we do not know how the user could remain substantially in control, and able to review the basis of a recommendation, if they cannot read the guidelines on which the recommendations are based.

N. Validation

**Comment:** One commenter suggested that we extend the guidelines to provide the recommended validation. In essence, these guidelines assume a basic level of validation for all MR-CDS software, and then recommend that heightened validation be used if the software takes over the decision-making from the healthcare professional.

**Response:** The Coalition does not want to venture into those waters. The types of validation required both for software that leaves the professional user in control, and for software that takes over the decision-making, span a vast range depending on the nature of the software and the intended use. Articulating the requirements for validation in those two circumstances is not something the Coalition feels prepared to do.

#### O. Learned dependence

**Comment:** One comment suggested that dependence does not simply come from the design of the software or from the intended use, but also from how the user chooses to rely on the software. This commenter suggested that certain people, particularly, for example, those who are young and grew up with digital tools, and also those who use software repeatedly and see good results, might consciously or unconsciously decide to rely more heavily on the software.

**Response:** While we believe this to be an accurate observation, it leads us beyond the scope of this task. The purpose of these guidelines is to identify best practices for software developers to ensure that users can reasonably review the basis for software recommendations, not to ensure that professionals will always do so when appropriate. The software developer's responsibility is to ensure that the user can undertake a reasonable review.

As to whether or not healthcare professional users do in fact always conduct a reasonable review when they should, that is a matter for regulation under the practice of medicine. State boards of medicine need to take steps to ensure that physicians are trained to conduct appropriate reviews of software recommendations, rather than merely rely on whatever they are told. This really becomes a practice of medicine issue, not one for these guidelines nor for FDA.

### III. **The Future**

The CDS Coalition is a temporary coalition created to seek improvements in the regulatory environment for clinical decision support software. As a consequence, the Coalition's objective will be to find a permanent organization that is interested in keeping these guidelines up-to-date in the future. We shall be actively looking for such an organization over the next year, and transfer that responsibility to the new organization once we identify it.

# **Voluntary Industry Guidelines for the Design of Medium Risk Clinical Decision Support Software to Assure the Central Role of Healthcare Professionals in Clinical Decision-Making**

Developed by the CDS Coalition

## **Background and Purpose**

In December 2016, Congress enacted the 21st Century Cures Act, adding a new subparagraph 520(o)(1)(E) on Clinical Decision Support (CDS) software to the Federal Food, Drug and Cosmetic Act. That new subparagraph carves out certain software from the scope of FDA regulation. Ultimately, the United States Food and Drug Administration (FDA) will be responsible for administering and enforcing that new provision.

Separately, over the last several years, many companies developing CDS software have been sorting through the various design options for empowering the user to take control of the decision-making. In this quest, some companies have been looking for guidelines on the proper approach to user engagement. Further, many companies are exploring the use of machine learning and other forms of artificial intelligence to power CDS software. But the adoption of those technologies brings with it the challenge of keeping the user in control of the decision-making.

For CDS software that FDA does not regulate, industry is best served by self-regulating through adopting basic software design guidelines. To that end, these guidelines are intended to foster the design of software in such a manner that healthcare professional users will be able to independently review the basis for the recommendations the CDS software produces, such that the professionals will not need to rely primarily on the recommendations. The purpose of these guidelines is to provide a unified approach that CDS software developers can employ to ensure they are providing at least a basic level of transparency and the opportunity to review the basis of the recommendations made.

At their core, these guidelines are intended to give software developers a framework for discerning whether additional validation – beyond that which they would ordinarily do – is required as a consequence of the software taking over decision-making from healthcare professionals. These guidelines reflect the view that taking over, in any substantial way, the healthcare decision-making carries with it heightened responsibility for validation.

New subparagraph 520(o)(1)(E) on CDS software addresses that same topic. As a statute, it establishes the minimum design elements necessary to avoid FDA regulation. These industry guidelines are not an attempt to simply apply that legislation, but rather establish voluntary industry guidelines for accomplishing those same objectives and more.

In the development of these guidelines, the statute was relevant in the sense that the Coalition wanted to establish guidelines that, if met, would assure that the software is not regulated by FDA. At the same time, the Coalition wanted to go beyond merely repeating the statute. Instead, the Coalition sought to identify guidelines that would more broadly assure some consistency in approach by software developers with regard to design features intended to assure the central role of healthcare professionals in clinical decision-making. The Coalition believes that leaving the healthcare professional in control helps to ensure the appropriateness of the clinical decision-making. Software that does not meet these guidelines can be quite safe and effective, but may require additional validation because of the risk that such software will supplant the judgement of healthcare professionals.

## The Meaning of “Voluntary Industry Guidelines”

Software developers do not need to follow these guidelines to avoid FDA regulation. There are other ways of meeting the requirements of the new subparagraph 520(o)(1)(E) on CDS software. However, these guidelines represent a safe harbor of sorts from FDA regulation. These guidelines are certainly not intended to be prescriptive, requiring that software developers design software in one way and one way only. Instead, they are an illustration of how software developers can achieve adequate empowerment of end-users. Software developers can depart from these guidelines, but we recommend that companies only dip below what these guidelines state based on reasoned justifications or based on validations that the software developer has conducted. Software that is adequately validated is less in need of ensuring the active role of the user in the decision-making. Software that does not meet these guidelines necessarily relies more on the proper functioning of the software over the judgment of the healthcare professional, and therefore may require more validation and potentially FDA oversight.

In addition, FDA, not industry and not these guidelines, will determine whether a given approach meets the requirements of the law. For general educational information only, the Coalition includes its analysis of the statutory requirements in Appendix D of these guidelines.

## Guideline Updates

CDS software is evolving fast. New technologies are coming along, for example, based on machine learning as well as novel clinical applications. Software itself is changing, with changes in the way humans interact with software, for example, moving away from clicking on links. Further, the regulatory environment is changing, with FDA announcing that it is likely to deregulate additional categories of software.

The Coalition plans to take a fresh look at these guidelines periodically to update them in areas where we learn more about best practices in user engagement, as well as changes in technology, clinical use and the regulatory environment. In the long run, because the Coalition is a temporary organization, we plan to look for a permanent home for these guidelines where they can be kept up-to-date.

## Scope of these Guidelines

As already noted, FDA will regulate high risk CDS software where, among other things, (1) the user does not have a reasonable opportunity to review the basis of a recommendation and (2) the software performs important functions where, should the software not work as intended, someone could get seriously hurt. Further, in our judgment, low risk CDS software where the risk of injury is low regardless of whether there is reasonable opportunity to review the basis for the recommendation need not be burdened by these guidelines. Instead, these guidelines focus on what we call “medium risk clinical decision support” software or “MR-CDS.” MR-CDS is software that:

- Uses patient-specific information and organized clinical knowledge;
- Performs some analysis using that information and knowledge (rather than simply displaying or transmitting the information);
- Produces a particular actionable recommendation (with or without additional recommendations) for the diagnosis, treatment or management of a disease or condition for a particular patient; and
- Is not an accessory to a medical device.

That last point is important in distinguishing MR-CDS software from software that is used in conjunction with a specific medical device to analyze the output of that device. MR-CDS software may well be incorporated into an electronic health record, for example, but so long as it is not an accessory to a medical device, it would fall within the scope of these guidelines.

“Actionable recommendation” means that the recommendations have the following characteristics:

- They are specific, not general. Specificity is important because healthcare professionals make specific decisions. General recommendations leave the healthcare professional the task of devising the specific action to be taken.
- They direct rather than merely inform. The recommendations have a degree of certainty associated with them. Certainty can be communicated by the software in a couple of different ways, from providing a singular recommendation to providing multiple recommendations, each with a degree of probability that strongly suggests that one particular recommendation is the right one. The key question is: does the software present at least one diagnostic or treatment decision that the user would conclude the software recommends?
  - Software which simply presents a range of alternative options does not convey the kind of certainty that would cause the software to be considered MR-CDS software for purposes of these guidelines.
  - Further, software that merely informs, as that concept is laid out in the policy paper entitled "Software as a Medical Device": Possible Framework for Risk

Categorization and Corresponding Considerations, is not included within the scope of these guidelines.<sup>2</sup>

- At the same time, software can provide multiple actionable recommendations if the software is addressing multiple conditions; for example, a primary recommendation, but also recommendations addressing comorbidities. So long as the recommendations are not presented in the alternative, the recommendations are actionable and therefore the software is within these guidelines.

These guidelines address the full range of healthcare decision-making from diagnosis to monitoring to therapeutic decision-making to triage. So long as the recommendation is actionable by the healthcare professional, and the other conditions are met, these guidelines would apply.

These guidelines further only address MR-CDS software intended for use by healthcare professionals.

## Overview of Voluntary Guidelines for Enabling Independent Review of the Basis for MR-CDS Recommendations

Healthcare professionals should be free to practice medicine to the best of their ability and in reliance on their own professional judgment, within the community standard of care. To empower medical professionals to use their best professional judgment, it is important that MR-CDS software enable healthcare professional users to independently review the basis of the recommendations the software makes. By so doing, the software developers can ensure that the healthcare professionals will not need to rely primarily on the software, but rather will be able to rely primarily on their own professional judgment.

Thus, to comply with these guidelines, developers must answer two fundamental questions affirmatively:

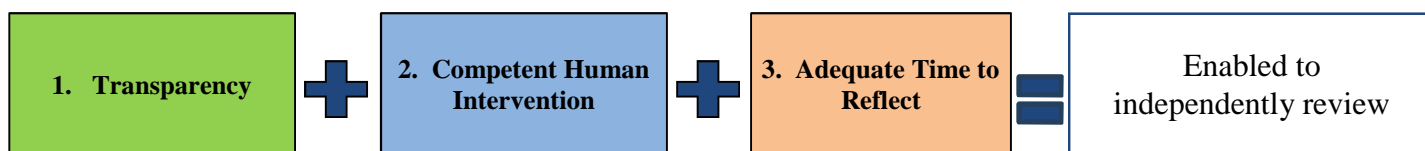
1. Are healthcare professional users able to independently review the basis of the recommendations the software makes?
2. Under the intended circumstances of use, will healthcare professional users not need to rely primarily on the software?

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<sup>2</sup> International Medical Device Regulators Forum, "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations, 18 September 2014; <http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf>

As already explained, software that does not meet these guidelines necessarily relies more on the proper functioning of the software in lieu of the judgment of the healthcare professional, and therefore may require a higher level of validation and potentially FDA oversight.

To answer the first of those two questions, MR-CDS software developers can use three criteria to determine if the MR-CDS is intended to enable the healthcare professional user to independently review the basis of the recommendations the software makes.



Each of these criteria would need to be met to enable the healthcare professional user to independently review the basis of the recommendations, as explained below.

1. **Transparency**. Does the software provide enough information for the user to understand and be able to evaluate the clinical basis for the software recommendation? This includes disclosure of the following:
  - a. What the software does and does not do. It is important in this regard that the labeling for the software communicate to the user the limits of the software’s functionalities. This means, among other things, including both the indications for use and contraindications in the labeling.
  - b. The information inputs used by the software. This includes (i) patient specific information, and (ii) the source of the clinical information or decision rules such as practice or professional guidelines that the software uses to analyze the patient information.

Furthermore, if a decision informed by the recommendation of the software could lead to serious injury, permanent impairment or death for the patient, the developer may also need to provide:

- c. An indication of the certainty or reliability of the output, including as appropriate, confidence levels and/or ranking of alternatives.
- d. The clinical rationale for the recommendations. This goes beyond merely identifying the source of the clinical rules, and includes a reasonable explanation of the clinical logic by which the software arrived at its specific recommendation based on patient specific information. This clinical rationale will vary greatly depending, for example, on whether the software is assisting with a diagnostic or therapeutic decision. The software communicates the clinical thought process behind the recommendation, not necessarily the computer science functionality used.

Most MR-CDS software is intended to aid a trained user in decision-making, but not to be a substitute for the user's expertise and judgment. On the other hand, if the MR-CDS software does not enable the intended user to sufficiently understand the recommendation made by the software and equally importantly, the basis for the recommendation, such MR-CDS software runs the risk of being used as a substitute for the user's expertise and judgment. In such cases, the software may need to be validated to a higher degree, and potentially subjected to FDA regulation.

This first criterion – transparency – requires more elaboration depending on the various types of data inputs and other design factors. As a result, the Coalition has developed specific design guidelines to ensure the transparency of MR-CDS software, and includes those in Appendix A of these guidelines.

- 2. Competent Human Intervention.** Is the intended user competent – through training, experience or otherwise - to make the clinical decision in question without the MR-CDS software? The education and experience required to be competent depends on the nature of the decision. A nurse, a primary care physician, and a specialist are each competent to make different types of decisions, as are pharmacists, home health aides and other health professionals and care-givers.

MR-CDS software intended to be used to extend a user's decision-making ability beyond his/her qualifications could mean that the healthcare professional is not able to independently review the basis for the recommendation. However, MR-CDS software that merely assists the user in applying her existing qualifications does enable independent review. MR-CDS software that, for example, collects, calculates, sorts, or otherwise gathers and presents information which the user is competent in interpreting (while easing the burden of data gathering or processing) should not, by itself, preclude the professional from independently reviewing the basis of the recommendations.

It is important to note that it may be prudent for decision-makers to also consider data outside of what the MR-CDS software has collected. Competent decision-makers will recognize that need and incorporate such information into their decision-making process. The labeling should elaborate on the limits of what the software itself can do, and the need to go beyond the software in certain cases. Further, if a decision informed by the recommendation of the software could lead to serious injury, permanent impairment or death for the patient, the labeling should also be clear about the necessary qualifications of the intended user.

Like the first criterion, this second criterion –competent human intervention– requires more elaboration depending on the various types of data inputs and other design factors. As a result, the Coalition has developed specific design guidelines to ensure competent human intervention, and includes those in Appendix B of these guidelines.

- 3. Sufficient Time to Reflect.** Based on the intended use, is the user expected to have enough time to reflect on the software output before making a decision? The amount of time available to reflect will depend on the acuity of the condition, and how much time can lapse before the patient receives medical care without risk. The amount of time needed to reflect may also depend on the complexity of the decision.



If the intended user does not have enough time to independently consider the data inputs, in practice, the user may not be able to independently review the basis of the recommendation. To qualify under these guidelines, if a decision informed by the recommendation of the software could lead to serious injury, permanent impairment or death for the patient, the labeling will need to be clear with regard to the environment in which the software is intended to be used, and whatever amount of time is needed to appropriately use, and double check the recommendations of, the software.

Like the previous two, this third criterion – sufficient time to reflect – requires more elaboration depending on the various types of data inputs and other design factors. As a result, the Coalition has developed specific design guidelines to ensure sufficient time to reflect, and includes those in Appendix C of these guidelines.

### A Mitigating Factor: Other Relevant Clinical Information

To answer the second of the two questions posed by these guidelines, after determining that a user is able to independently review the basis for a recommendation, when assessing a user's need to rely primarily on MR-CDS software, the manufacturer can take into account the likelihood that the user has access to other useful sources of clinical information concerning the individual patient useful to making the diagnostic or treatment decision. Access to information about the patient outside of the MR-CDS software mitigates the need of the user to rely primarily on the recommendations from the software.

In cases where the software inputs include all the relevant information concerning the individual patient, this simply means the same as the inputs portion of the transparency criterion above – the user has access to all of the information concerning the individual patient that has been inputted into the software available for direct review. In other words, this becomes redundant with the transparency criterion.

But in cases where the software considers a narrower set of inputs concerning the individual patient, this means the decision maker has access to additional information concerning the patient helpful to the decision. For example, it may mean the patient is available to the physician for direct physical examination, or that the physician is likely to have direct access to additional, useful diagnostic information such as radiological images or laboratory test results. If access to such information is important and useful, the labeling for the software should note the importance of considering those other information sources.

The bottom line is that the manufacturer can take into account, when assessing possible reliance by the user on the software, whether the user is likely to have available to her additional information outside of the MR-CDS recommendation concerning the individual patient to independently arrive at the particular decision. To be clear, the developer must still assure the healthcare professional users are able to independently review the basis of the recommendations the software makes. This additional information merely helps the software developer assure

that, in the end, the user does not need to rely primarily on the software for making the decision, and the second condition is therefore met.

# Appendix A

## Transparency Guidelines

If a given piece of software meets the Guidelines below, the transparency criterion under the test for determining whether software enables the user to independently review the basis for its recommendations would be met. To assure that healthcare professionals are able to independently review the recommendations of the software, as explained above, developers will also need to assure that they target appropriate healthcare professionals and use cases, and that users can be expected to have adequate time to reflect.

The Coalition recognizes that there may be other means to achieve transparency for the software in lieu of the steps recited below. These Guidelines are not intended as rigid requirements, but rather as a high level framework for manufacturers to follow. Manufacturers should analyze the purposes of these various guidelines and think about how the objectives can best be achieved for their particular software.

These Transparency Guidelines address two general questions:

1. What needs to be disclosed? We discuss four (4) types of disclosures:
  - i. The intended use, including both the indications for use and the contraindications
  - ii. The patient information and sources of clinical content used by the software
  - iii. The software output or recommendations
  - iv. The clinical rationale for the output or recommendation
2. How does it need to be disclosed?

Part of the complexity that these guidelines must face is that the information inputs can come in a wide variety of forms, and the recommendation outputs can likewise take many different forms. Without limiting the appropriate inputs and outputs, examples include:

Category of Information	Examples
Patient-specific information	<ol style="list-style-type: none"><li>1. Data from electronic health record automatically transferred</li><li>2. Data manually entered by patient</li><li>3. Data manually entered by the user</li><li>4. Data manually entered by another healthcare professional, not the user</li></ol>
Medical knowledge	<ol style="list-style-type: none"><li>1. Peer-reviewed medical literature, either individual articles curated for this purpose or commercially-available databases of such literature</li><li>2. Medical abstracts from meetings</li><li>3. Consensus clinical guidelines from medical societies</li></ol>

	<ol style="list-style-type: none"> <li>4. Institution specific clinical guidelines</li> <li>5. Expert medical opinions from individual professionals</li> <li>6. Medical insights gleaned by software using machine learning, through digesting raw medical data from a given population of patients</li> <li>7. Proprietary algorithms and calculators developed by drug or medical device companies</li> <li>8. Clinical trial results not vetted through peer reviewing</li> <li>9. Commercial clinical resources that aggregate and synthesize medical research and evidence</li> </ol>
Recommendations	<ol style="list-style-type: none"> <li>1. Quantitative calculated indices</li> <li>2. Qualitative likely diagnosis</li> <li>3. Qualitative likely best treatment option</li> <li>4. Qualitative diagnostic or treatment options with quantitative rankings</li> </ol>

These guidelines thus must contemplate all of those possible scenarios.

### Proposed Disclosures by Number of Required Clicks

Most software, when it comes to presenting information to the end-user, is designed to have multiple access levels represented by the number of clicks required to access the relevant information. These access levels permit the end-user to go deeper and deeper into the details as the user clicks on links that take the user ultimately to source information.

When it comes to ensuring transparency, the goal is to balance the need to avoid clutter with the need to reveal important information. With regard to the various elements required for transparency, in the table below, the guidelines set forth risk-based guides with regard to how many clicks should be necessary to get to the particular level of information, starting from either the page on which the recommendation is found, or an earlier page that the user will necessarily review before getting to the recommendation. For example, some software is designed so that the user is required to review an input page before getting to the recommendations. In that case, information regarding those inputs would be measured as against that input page.

- Click 0 means the information must be provided on the same page on which the inputs are recorded or the recommendation itself is provided
- Click 1 is a page that directly links to the input or recommendation page
- Click 2 is a page that directly links to a click 1 page

## Importance of Change Management

It is highly likely that the basis for the recommendations made by the software will evolve over time. While it is beyond the scope of the guidelines to provide detailed guidance on how to manage those changes, managing those changes is extremely important from a transparency standpoint. The transparency elements described below must be kept up-to-date as the basis for the software recommendations evolves. And it will take a very deliberate change management program to ensure that occurs.

## A General Comment on Labeling

We recognize that much MR-CDS software is incorporated into EHRs, and therefore the users do not encounter the MR-CDS software in the same way that they would if they were to use a freestanding software program. It operates more behind the scenes. That is why as we identified important labeling statements, we acknowledge that they might need to be one click away. In other words, there may an initial user interface that contains very little information, but there should be a link that allows the user to directly access basic information about what the software is and what it does.

Transparency Element	Clicks
<p><b>1. Disclosure of the intended use.</b></p> <p>a. In instructions for use contained in the software, the software should explain clearly:</p> <ol style="list-style-type: none"> <li>i. The role in the clinical practice that the software is to play.</li> <li>ii. Limitations on the use of the software, and in particular warnings and contraindications about not using it too broadly.</li> <li>iii. The intended user, as precisely as possible.</li> <li>iv. Information outside the software that the user may wish to consider.</li> </ol> <p>b. In promotional materials aimed at prospective buyers, in addition to those topics, the promotional materials should communicate:</p> <ol style="list-style-type: none"> <li>i. The intended use setting, as precisely as possible, and</li> <li>ii. Whatever amount of time is needed to appropriately use, and double check the recommendations of, the software.</li> </ol>	1
<p><b>2. Disclosure of information inputs</b></p> <p><b>a. Patient specific data</b></p> <ol style="list-style-type: none"> <li>i. Data the user enters manually into the MR-CDS program is presented back as a confirmation screen.</li> <li>ii. Data entered by access to an electronic record is: <ol style="list-style-type: none"> <li>1. Defined precisely by reference to the specific electronic record(s).</li> </ol> </li> </ol>	1
<ol style="list-style-type: none"> <li>2. Presented to the user in one or more screens with regard to the data that the software deems relevant for its recommendation.</li> </ol>	2
<p>b. <b>Clinical intelligence content.</b> Such content can come from many different sources, and those sources raise different issues. There are two different purposes served by the disclosures under this section: (1) allowing the user to understand and gauge the credibility, quality, completeness and appropriateness of the source of the content; and (2) allowing the user to review the original source material for the clinical content such that they can conduct their own review of the basis for the recommendation. Thus, in addition to providing the clinical rationale under part 4 below, the software must disclose the source or sources, as applicable, of its clinical intelligence as follows:</p> <p><b>i. Databases.</b> Examples include commercially available databases such as MEDLINE®, and databases of clinical content curated specifically for the purpose of the software.</p> <ol style="list-style-type: none"> <li>1. To be transparent, the software must provide enough information for the user to evaluate the database for completeness, currentness, quality, and relevance.</li> <li>2. The database should be accessible to the user, but need not be within 2 clicks.</li> </ol>	1 unless 2 is specified

Transparency Element	Clicks
<ul style="list-style-type: none"> <li>ii. <b>Specific, written, published materials.</b> Examples include journal articles and medical society guidelines. <ul style="list-style-type: none"> <li>1. To be transparent, the software must provide enough information for the user to find the published materials.</li> <li>2. Options for providing published materials. <ul style="list-style-type: none"> <li>A. If the materials are provided through the software, they should be within 2 clicks of the clinical content page.</li> <li>B. If they are not provided, they should be reasonably accessible to the user. Further, the time required to access them must be considered under the time for reflection guidelines below.</li> </ul> </li> </ul> </li> <li>iii. <b>Specific, written, unpublished materials.</b> Examples include clinical guidelines unique and proprietary to the developer or user institution. <ul style="list-style-type: none"> <li>1. The full text of such written materials needs to be provided within 2 clicks.</li> <li>2. The text must be accompanied by a brief explanation of the source of the materials and how they were developed, including, for example, the authors and their qualifications.</li> <li>3. The software also should disclose any financial interest in the recommendation held by the individual or institution, akin to the disclosures required in FDA’s Good Reprint Practices.</li> </ul> </li> <li>iv. <b>Content that has not been summarized.</b> Examples include software-embodied algorithms based on input received from a clinical expert or committee of experts, or from machine learning applied to raw data. <ul style="list-style-type: none"> <li>1. <b>If the source is people,</b> such people need to be described by reference to their qualifications for the task. Again, the purpose of this transparency is to allow the user to assess the credibility and qualifications of the source. The summary should also include the particular topics on which these experts gave input.</li> <li>2. <b>If the source is machine learning or otherwise not human,</b> the software must provide the user with appropriate metrics to give the user an understanding of the accuracy of the source. In language that is understandable to a clinician who does not have software development expertise, the program must contain a page that explains how the software has been validated, and provides meaningful quantitative</li> </ul> </li> </ul>	

Transparency Element	Clicks
<p>assessments of the accuracy of the software. If in fact there is little data to support the accuracy of the software, the software must clearly state that. The software should provide a thorough explanation of the data sets used to feed and test the machine to provide important context and assurance to the clinician. The discussion should include any limitations or potential biases in the methods used to gather the data. Further, the software should explain if the machine learning model is designed to be adaptive, using both retrospective and prospective data inputs for incremental evolution of the decision algorithms for improving the accuracy. This page should be regularly updated as the software matures.</p>	
<p>Furthermore, depending on the role of the software and the risk associated with the intended use, the developer may also need to provide additional information. The following information is necessary if a decision informed by the recommendation of the software could lead to serious injury, permanent impairment or death for the patient. That determination should be based on an analysis of:</p> <ul style="list-style-type: none"> <li>A. Significance of the information provided by the SaMD to the healthcare decision, and</li> <li>B. State of the healthcare situation or condition.</li> </ul>	
<p>3. <b>Disclosure of the output.</b> The software must disclose enough to fully reflect the variability and uncertainties of medicine.</p> <ul style="list-style-type: none"> <li>a. <b>Qualitative outputs from an expert system</b> <ul style="list-style-type: none"> <li>i. The software must provide the full range of possible recommendations reasonably derived from the clinical inputs. In determining what is reasonably derived from clinical inputs, it is also important to consider the severity of a particular possibility. A possibility with a very high severity may need to be disclosed even though the risk of it being true is low.</li> <li>ii. In addition, if the software developer would like, the software developer may identify a primary recommendation or suggest a ranking or confidence statements that need to be supported by the clinical rationale described below in section 4.</li> <li>iii. Note, if the software presents a range of possibilities but without any associated ranking or confidence statements, the software likely is not the type of MR-CDS software that is covered by these guidelines.</li> </ul> </li> <li>b. <b>Quantitative outputs from an expert system</b> <ul style="list-style-type: none"> <li>i. Using appropriate statistical tools, the software must</li> </ul> </li> </ul>	0



Transparency Element	Clicks
<p>communicate results, allowing the end user to determine the accuracy and reliability of the results presented.</p> <p><b>c. Machine learning outputs</b></p> <ul style="list-style-type: none"> <li>i. The software must provide the full range of possible recommendations reasonably derived from the clinical inputs.</li> <li>ii. In addition, if the software developer would like, the software developer may identify a primary recommendation or suggest a ranking or confidence statements that need to be supported by the clinical rationale described below in section 4.</li> <li>iii. If a recommendation is presented as a singular option, the recommendation must be accompanied by the associated confidence level, together with an assessment of both the likely benefits and risks.</li> </ul>	
<p><b>4. Disclosure of the clinical rationale for the recommendations or rankings.</b> In addition to describing the source of its clinical knowledge under part 2 above, the software must identify the particular clinical rationale that serves as a basis for each recommendation. If software uses more than one source, each source should be identified. Specifically, wherever possible the software should reveal which particular sources were used for a particular recommendation and the role they played in supporting the recommendation.</p> <ul style="list-style-type: none"> <li>a. <b>Qualitative outputs from expert systems.</b> The software must provide an explanation of the clinical reasoning such that the end user can understand the clinical rationale underlying the recommendation. <ul style="list-style-type: none"> <li>i. If based on specific <b>clinical guidelines</b>: <ol style="list-style-type: none"> <li>1. An explanation of the clinical decision pathway through the guidelines. This may include decision trees, flow diagrams or other visual models.</li> <li>2. A summary of any additional considerations factored into the recommendation beyond what was stated in the guidelines.</li> <li>3. An explanation of any deviations from the published guidelines.</li> </ol> </li> </ul> </li> </ul>	1
<ul style="list-style-type: none"> <li>ii. If based on specific <b>published literature</b>: <ol style="list-style-type: none"> <li>1. Identification of the specific literature that underlies the recommendation. If multiple articles address the recommendation, the software should present up to three that support the recommendation, as well as up to three that present a contrary view (if any).</li> <li>2. A summary of the clinical reasoning based on the factors identified in those articles.</li> </ol> </li> </ul>	1

Transparency Element	Clicks
<p>3. Copies of the identified articles. If the developer elects not to provide copies directly, the time associated with the user being able to obtain copies must be factored into the time for reflection.</p>	2
<p>iii. If based on <b>any other source</b>, provide:</p> <ol style="list-style-type: none"> <li>1. An explanation of the clinical thought process, including any assumptions that underpin the recommendation to a degree typical of a second opinion.</li> <li>2. A description of the clinical evidence, if any, that supports the recommendation, to the degree typical of a medical abstract, or an appropriate reference to published evidence.</li> </ol>	1
<p><b>b. Quantitative output from expert systems</b></p> <ol style="list-style-type: none"> <li>i. The full and precise mathematical formulae used in the calculation.</li> <li>ii. A narrative explanation of the source or clinical basis for each step in the calculation, or a reference to the source of the formula.</li> <li>iii. For any such source, follow any relevant disclosure above in part 4.a. for qualitative information.</li> </ol>	1
<p><b>c. Machine learning outputs</b></p> <ol style="list-style-type: none"> <li>i. Software built on machine learning needs to explain that it has spotted an association through machine learning, and state as precisely as it can the association. For example, with regard to a particular patient, the software might note that there is an association between patients with X, Y, and Z symptoms and improvements in those symptoms when taking Drug A.</li> </ol>	1

## Appendix B

### Competent Human Intervention Guidelines

If a given piece of software meets the Guidelines below (as well as transparency and time-to-reflect Guidelines defined in separate appendices), under the CDS Coalition's guidelines, the healthcare professional would be able to independently review the basis for the recommendation. These Guidelines are not intended as requirements, but rather, as one approach for determining whether the healthcare professional is able, by virtue of education and experience, to independently review the recommendations of the software. The Coalition recognizes that there may be other means to demonstrate competent human intervention.

These Guidelines recognize the need of a healthcare professional to exercise his/her clinical expertise and judgment within his/her applicable practice area and utilizes traditional licensure classifications. To enable the end user to independently review the basis of the recommendations, the software should be intended to be used to support a decision the user is qualified to make without the use of the software. Consequently, software intended to be used to extend a user's decision-making ability beyond his/her qualifications, license, certification or practice area would not ensure that the user is able to independently review the basis for the recommendations.

#### **I. Competent Human Intervention Definition**

Competent human intervention means the intended user must possess any necessary knowledge, skill, judgment, training, experience and license to understand the information presented, appreciate the consequences of acting or not acting on that information and make a decision or take action based upon the information presented.

In determining the level of knowledge, skill, judgment, training, experience and license necessary to qualify as competent human intervention, we look at (1) the abilities and licensure of the intended user and (2) the nature and complexity of the clinical decision-making process.

#### **II. Competent Human Categories**

We outline three categories of intended healthcare professional users below.

Ancillary Care Provider is typically a non-physician professional who provides clinical or other healthcare service to individuals and has been trained and certified or licensed in her profession. Ancillary Care Providers may have a variety of degrees and specialties, including but not limited to registered nurses, nurse practitioners, physician assistants, radiology technicians, pharmacists, midwives, dietitians, therapists, psychologists, chiropractors, phlebotomists, physical therapists, respiratory therapists, occupational therapists, audiologists, speech pathologists, optometrists, emergency medical technicians, paramedics, medical laboratory scientists, and medical prosthetic technicians.

Primary Care Provider is typically a person who is legally qualified and validly licensed to practice medicine as a primary care physician. Primary care means providing continuing and comprehensive medical care to individuals and families, not limited by the cause, organ system or diagnosis and includes the specialties of internal medicine, family medicine, general practice and pediatrics. In some cases provided by law, within specific areas of practice, Primary Care Providers can include non-physicians such as nurse practitioners, physician assistants, pharmacists.

Specialty Care Provider is a physician who is board certified in a particular specialty or sub-specialty by the American Board of Medical Specialties, other than internal medicine, family medicine, general practice or pediatrics.

This is a particularly fluid area of this proposal as laws change with regard to professional licensing and oversight. This break down into three categories is more intended to convey simply a three-tiered framework for considering professional competence, in an effort to make sure that the software is targeted to generally the right level.

We recognize that MR-CDS software may, for example, be inserted into an EHR and therefore broadly available to a number of different users. If the MR-CDS software is low risk enough as explained in part V below, no special labeling is required and there is no issue of targeting the appropriate end user. But if the use of the software is higher risk, then the software vendor would either need to follow these guidelines, or potentially subject the software to extra validation and potentially FDA oversight. In an effort to follow the guidelines, the software developer could design the software, for example, to limit access to physicians or whatever the appropriate level of competence. For example, perhaps the software could be designed to only be accessible when the user logs in with an ID that indicates that the person is a physician. We are quite sure that creative people can come up with other approaches to limit the intended user.

### **III. Clinical Decision Support Categories**

We outline the three corresponding categories of decision support based upon the nature and complexity of the clinical decision-making process.

**Care Management MR-CDS** is defined as tools that support routine clinical decisions related to the execution or management of a care plan that requires basic clinical knowledge, simple triage decisions or other determinations of when the intervention of a general practitioner or specialist is recommended. Care Management MR-CDS does not involve diagnostic or treatment decision-making.

**Primary Care MR-CDS** is defined as tools that assist general practitioners in making a diagnosis, selecting a treatment or therapy, developing a medical treatment plan, or help general practitioners determine whether the intervention of a specialist is recommended.

**Specialist MR-CDS** is defined as tools that (1) address those diagnostic and treatment decisions involving diseases or conditions, types of patients or methods of treatment that required specialized knowledge gained through advanced medical training or (2) identifies when a different specialist or sub-specialist is recommended.

#### **IV. Competencies and Decision Type Combinations That Allow For Independent Review**

Combining those factors, the Xs indicate where independent review of the basis of the recommendation by the software is possible because there is competent human intervention.

	<b>Ancillary Care Provider</b>	<b>Primary Care Provider</b>	<b>Specialty Care Provider</b>
<b>Care Management</b>	X	X	X
<b>Primary Care Services</b>		X	X
<b>Specialist Services</b>			X

Thus, when the user is intended to be an ancillary care provider, only the very basic care management decisions can be supported through MR-CDS software without the need for considerable validation and potentially FDA oversight.

#### **V. Intended Use Requirements in Labeling and Promotional Activities**

To qualify as intended for use by people who can act as competent human intervention, the labeling should elaborate on the limits of what the software itself can do, and the need to go beyond the software in certain cases. Further, if a decision informed by the recommendation of the software could lead to serious injury, permanent impairment or death for the patient, the labeling should also be clear about the necessary qualifications of the intended user.

In addition, manufacturers' promotional practices must be consistent with the notion that the MR-CDS software is intended to be used by applicable intended users. This means that the sales and marketing activities are targeted at only the applicable intended user category. By way of example, the tradeshow attended, magazine and media outlets in which the product is advertised and invitees for meetings or presentations should be consistent with and reflect the applicable intended user for such product.

# Appendix C

## Time to Reflect Guidelines

If a given piece of software meets the Guidelines below (as well as transparency and competent human intervention guidelines defined in separate appendices), under the CDS Coalition’s guidelines, the healthcare professional would be able to independently review the basis for the recommendation. These Guidelines are not intended as requirements, but rather, as one approach for determining whether the healthcare professional is able, by virtue of having enough time to reflect, to independently review the recommendations of the software. The Coalition recognizes that there may be other means to demonstrate adequate time to reflect.

To enable the end user to independently review the basis of the recommendations, the software must be intended to be used in a setting that allows the user sufficient time to evaluate and consider the MR-CDS output before making a decision or taking an action. Consequently, software intended to be used in a clinical setting where the acuity of the condition combined with the complexity of the decision-making does not allow the user the amount of time necessary to reflect on the output would not ensure that the user is able to independently review the basis for the recommendations.

### I. “Time to Reflect” Definition

Time to reflect means the intended user has the amount of time necessary to evaluate the basis of the recommendation of the software before taking action. In determining whether there is sufficient time to reflect, we examine two factors: (1) the acuity of the condition and (2) the complexity of the clinical decision-making process.

### II. Acuity of the Condition

The acuity level is the time that can lapse without material risk to the patient before that patient receives medical care. Acuity levels can be classified as follows:

**Immediate.** There is no time for reflection. This acuity level refers to conditions that could result in death or serious irreversible injury or where there is imminent risk of deterioration to such condition if there is any delay in treatment or intervention.

**Urgent.** Treatment is time-sensitive. This acuity level refers to conditions that could result in death or serious irreversible injury or where there is risk of deterioration to such condition or requiring emergency care if treatment or intervention is not commenced promptly and without undue delay. Urgent conditions generally require treatment within a fifteen minute to two hour timeframe.

**Non-Urgent.** There is sufficient time for reflection. This acuity level refers to conditions for which investigation or interventions can be delayed or referred to another healthcare provider or health care system without risk of death, serious irreversible injury or deterioration requiring emergency care.

### III. Complexity of the Clinical Decision-Making Process

The complexity of the clinical decision-making refers to the amount of time the user needs to understand the clinical rationale underlying the decision and evaluate it for accuracy.

**Simple.** The clinical decision-making process or clinical rationale for such decision is so well established, or the calculation is so easily understood, that the software output can be evaluated nearly instantaneously without review of detailed supporting materials.

**Moderate.** The clinical decision-making process or clinical rationale for such decisions is such that the software output can be understood with minimal consideration or quick reference to detailed supporting materials.

**Complex.** The clinical decision-making process or clinical rationale for such decision is so complicated, multifaceted or multifactorial in nature that the software output requires an extended time to be evaluated, or needs to be interpreted in connection with the detailed supporting materials.

In connection with this factor, the software developer must also consider how quickly, with the software, the user can consult the underlying guidelines that serve as a basis for the recommendation by the software.

### IV. Acuity and Complexity Combinations That Allow For Independent Review

Combining those factors, the Xs indicate where independent review of the basis of the recommendation by the software is possible because there is adequate time for reflection.

	<b>Immediate</b>	<b>Urgent</b>	<b>Non-Urgent</b>
<b>Simple</b>	X	X	X
<b>Moderate</b>		X	X
<b>Complex</b>			X

Thus, when the acuity of the situation is immediate, only the very simple forms of decision-making can be supported through MR-CDS without the need for considerable validation and potentially FDA oversight.

Many MR-CDS programs may cover a range of acuity and complexity. In determining how to treat a given MR-CDS program, the developer should focus on the highest risk use – the highest combination of acuity and complexity. Alternatively, the developer can employ strategies to separate out the software functions, so these guidelines need only be followed to the appropriate degree for the risk associated with the particular functionality.

## **V. Intended Use Requirements in Labeling and Promotional Activities**

To qualify under these guidelines, if a decision informed by the recommendation of the software could lead to serious injury, permanent impairment or death for the patient, the labeling will need to be clear with regard to the environment in which the software is intended to be used, and whatever amount of time is needed to appropriately use, and double check the recommendations of, the software.

In addition, manufacturers' promotional practices should be consistent with the notion that the MR-CDS software is intended to be used within a certain time for reflection given the complexity of the decision. This means that the sales and marketing activities describe the typical medical care setting where the MR-CDS software will likely be used, and the complexity of the decision-making.



# Appendix D

## Background: Understanding the Statute

As explained above, these guidelines are not meant to be an interpretation of the new statute. But at the same time, the goal of the Coalition is to ensure that compliance with these guidelines also means that the software is not FDA-regulated. Thus, an understanding of what the new statute requires is foundational to the development of these guidelines. To provide that understanding, in the table below in the left-hand side we include the new language from the statute, and on the right-hand side provide a running commentary explaining the significance of the language.

Language of the new subparagraph 520(o)(1)(E) of the Federal Food, Drug And Cosmetic Act	Commentary
(1) The term device, as defined in section 201(h), shall not include a software function that is intended—	Paragraph (1) of subsection (o) lists a variety of software functions that are excluded from the FDA definition of a medical device. Because this document focuses on clinical decision support software, we focus our analysis on subparagraph (E) that includes CDS.
(E) unless the function is intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system,	<p>The introduction to subparagraph (E) is a bit jarring to read, because it starts with an exclusion. Think of it as a double negative. These are software functions that are <u>not</u> <u>ex</u>cluded from the FDA definition of a medical device.</p> <p>We have used formatting to make this introductory clause easier to comprehend.</p> <p>For decades, FDA has regulated software that analyzes medical images and certain signals from electronic medical devices.</p> <p>The term “medical image” is fairly clear. There are a wide variety of file formats routinely used for medical images, but the key is that the file represents an image used for a medical purpose. So conceivably, this could include a simple JPEG, if the photograph is, for example, of a mole and the software is being used to analyze that photograph of a mole for assessing the possibility of melanoma.</p> <p>The term signal probably refers to an electronic</p>

Language of the new subparagraph 520(o)(1)(E) of the Federal Food, Drug And Cosmetic Act	Commentary
	<p>signal, and such signals typically are defined as an electric current that represents information. There are two basic types of electrical signals: analog and digital. In analog signals, some continuously variable aspect of the electrical current represents the information.</p> <p>In vitro diagnostic device is a well-defined term in FDA regulation.</p> <p>A signal acquisition system is a commonly used phrase in electrical engineering.</p> <p>The essence of this exclusion seems to be electronic information that is not comprised of either words or numbers understandable by humans, but rather visual or graphic information requiring interpretation.</p>
for the purpose of—	<p>This phrase then marks the introduction of the types of software that are in fact excluded from the FDA medical device definition. Excluded software must meet all three of the following criteria (notice the word “and” after the second criterion.)</p>
(i) displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);	<p>This first criterion is very broad. Indeed, it can be boiled down for our purposes to software that “analyzes” “medical information.”</p> <p>Given our focus on clinical decision support software, we will not analyze the “display” or “printing” functionality portions of this section.</p> <p>Clinical decision support typically involves taking generalized knowledge and applying it to a specific patient. Congress drafted this language to include the analysis both of the generalized medical information, as well as its application to the particular patient.</p> <p>It is noteworthy that the parenthetical is merely an example, and not words of limitation. The information does not need to be from either peer-reviewed clinical studies or medical</p>

Language of the new subparagraph 520(o)(1)(E) of the Federal Food, Drug And Cosmetic Act	Commentary
	<p>practice guidelines. The key statutory phrase is the wide open description of “other medical information.” Other than the information being medical, there is no limitation on the scope of that language.</p> <p>Thus the generalized medical information can come from a wide variety of sources, ranging from broadly accepted medical information to brand-new medical insights that have not been affirmed in any way by the medical establishment.</p> <p>Notice that the example “clinical practice guidelines” is not limited to consensus guidelines or the guidelines of established medical societies. Thus, even that example suggests that any guidelines, even if they are only specific to a particular medical provider, qualify.</p> <p>Beyond that, the open-ended reference to “other medical information” would include such sources as individual medical opinions of healthcare professionals, to new medical insights derived by analyzing large troves of patient data. There is simply no limit in the statute on what qualifies as medical information.</p>
<p>(ii) supporting or providing recommendations to a healthcare professional about prevention, diagnosis, or treatment of a disease or condition; and</p>	<p>This subparagraph squarely focuses on the function of clinical decision support software, in that the core purpose of such software is to provide or support recommendations for clinical decisions.</p> <p>This subparagraph also makes it clear that the threshold for the applicability of this entire provision is that the software must be directed toward recommendations for healthcare professionals, as opposed to consumers and patients.</p> <p>The phrase “about prevention, diagnosis, or</p>

Language of the new subparagraph 520(o)(1)(E) of the Federal Food, Drug And Cosmetic Act	Commentary
	treatment of a disease or condition” focuses the section on software that might otherwise qualify as a medical device, as that language is taken out of the medical device definition.
(iii) enabling such healthcare professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such healthcare professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.	<p>This is the meat of the subparagraph, and the toughest part of the test.</p> <p>The word “enabling” is one of the most important words in this particular subparagraph. The software has to be designed and marketed so as to “enable” healthcare professionals to independently review the basis for the recommendations. So we have to ask ourselves what it takes for healthcare professionals to be so enabled.</p> <p>For healthcare professionals to be able to review the basis for the recommendations, implicitly the software must meet at least three conditions:</p> <ol style="list-style-type: none"> <li>1. The healthcare professional has to be qualified to review the basis for the recommendation. In other words, it is not enough that someone is simply generically a healthcare professional. More specifically, the particular healthcare professional has to be qualified to conduct an independent review of the particular recommendation. So a psychiatrist, even though she is a healthcare professional, may not be qualified to review a recommendation by the software with regard to the treatment of cancer. The particular recommendation at issue has to be within the scope of competence of the healthcare professional targeted by the software.</li> <li>2. The healthcare professional must have the time necessary to conduct the independent review. If the software focuses on a time critical function such</li> </ol>

Language of the new subparagraph 520(o)(1)(E) of the Federal Food, Drug And Cosmetic Act	Commentary
	<p>as determining whether to shock a patient with an external defibrillator in the face of an urgent arrhythmia, to meet this criterion the basis for the recommendation would need to be very simple and susceptible to being reviewed in the amount of time available.</p> <p>3. The healthcare professional must be given access to the medical information – both patient specific and generalized – on which the recommendation is based so that the professional can review that basis. We refer to this concept as transparency, meaning the ability to see through the software to the underlying information.</p> <p>A substantial portion of these industry guidelines focuses on amplifying the meaning of those three factors.</p> <p>But there is a second, in a sense parallel, requirement in the section. That second requirement is that it is not the intent of the software developer for the user to “rely primarily on any of such recommendations.” In some cases, this seems like a redundant statement of the test, in that if the software gives healthcare professionals complete latitude to independently review the basis, then the user is not intended to “rely primarily on such recommendations.” However, statutory language is never dismissed as simply redundant if there is an additional meaning which it can be reasonably given. And in this case, there is another factor that should be considered.</p> <p>That factor is whether there is information beyond what the software provides on which the healthcare professional can base her therapeutic or diagnostic decision. The</p>

Language of the new subparagraph 520(o)(1)(E) of the Federal Food, Drug And Cosmetic Act	Commentary
	<p>existence of such additional information makes the healthcare professional less reliant on the recommendation from the software.</p> <p>When making a diagnostic or therapeutic decision, healthcare professionals typically consider a wide range of information including direct physical examination of the patient, a medical history that the healthcare professional might take during an interview of the patient, laboratory tests that the healthcare professional may review directly and other such information. The existence of such information, so long as it is available to the healthcare professional, makes the healthcare professional less reliant on the software's recommendation. To be sure there may not always be such additional information in this age of digital health care, but if there is such additional information, the availability of that information should be considered.</p> <p>The bottom line is that there are two ways to make it so that a healthcare professional is not primarily reliant on the software's recommendation:</p> <ol style="list-style-type: none"> <li>1. Access to all of the information on which the software bases its recommendation,</li> <li>2. Access to other information outside of that considered by the software.</li> </ol> <p>Both of those, considered together, will make a healthcare professional who is qualified to make a decision, and who has adequate time to make that decision, less reliant on the software's recommendation.</p> <p>Thus, these need to be considered together, and to some extent complement each other. If software is absolutely transparent in that the healthcare professional has very quick and easy</p>

Language of the new subparagraph 520(o)(1)(E) of the Federal Food, Drug And Cosmetic Act	Commentary
	<p>access to all of the information on which the software bases its recommendation, that by itself will demonstrate that the healthcare professional is not intended to primarily rely on the recommendation. But if that transparency is not so complete or so easily accomplished, then the developer may consider whether other complementary information that the healthcare professional can reasonably be expected to have outside of the software, considered together, means that the healthcare professional is not intended to rely primarily on the software's recommendation.</p> <p>At the same time, it must be recognized that the sentence construction makes it clear that the statute principally looks to the ability of the healthcare professional to independently review the basis of the recommendation in determining that the healthcare professional is not primarily reliant on the software. So while information the software does not consider – information that is directly available to the healthcare professional – can help accomplish the ultimate objective of avoiding primary reliance, it cannot compensate for software that does not allow for the review of the basis for its recommendation. The statute requires that the healthcare professional be able to review the basis of the recommendation. Outside information simply makes it easier to attain the ultimate goal of avoiding reliance.</p>