May 30, 2014

VIA EMAIL

Bakul Patel, MS, MBA
SaMD Working Group Chair
International Medical Device Regulators Forum

Comments to "Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Controls"

Dear Mr. Patel,

The International Medical Device Regulators Forum (IMDRF) issued a revised version of a proposed framework for the regulation of Software as a Medical Device (SaMD) on March 26, 2014. The document was titled "Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Controls" (the IMDRF Proposal). On behalf of the mHealth Regulatory Coalition (MRC) and the Clinical Decision Support Coalition (CDS Coalition), we would like to offer these comments to the IMDRF Proposal. We hope our comments will aid IMDRF and its member regulators as they develop and refine their approach to the regulation of SaMD.

While not very traditional for a letter of this sort, we must start with a confession. When IMDRF commenced this work item, we were frankly skeptical that it would be productive. We had concerns that the topic was in some ways too big, too complicated and too ill defined for the international community to be able to effectively develop a consensus. Simply put, IMDRF has proven us wrong. The forum has made substantial progress in thinking through these issues. We appreciate the work that IMDRF has done and we are confident that the forum's work will aid regulators and the health information technology (HIT) industry across the globe.

As a bit of background, the MRC is a diverse group of mobile healthcare technology stakeholders focused on promoting the development of an open, realistic, and thoughtful regulatory policy perspective on mobile health technologies. The MRC members include medical device manufacturers, smartphone healthcare application developers, cellular handset manufacturers, network operators, and back end software services and data storage providers, as well as representatives of provider organizations, clinicians, healthcare researchers, and other industry and trade associations. Our members share the common goal of promoting a balanced approach between regulatory policies that protect the public and insure patient safety, and the need for innovation and getting new products to the market for patients' best interests.

Likewise, the CDS Coalition is also a diverse group of stakeholders consisting of software providers, IT infrastructure manufacturers, healthcare payers, hospitals and other providers, medical device manufacturers, trade groups, and members of the clinical community who represent patients and professional clinical societies. The CDS Coalition's focus is, not surprisingly, clinical decision support software (CDS). CDS is a critical aspect of healthcare today and is increasingly important as medical data and individual patient information become more readily available electronically. Volumes of patient data are being generated from medical devices, health information systems and other sources every day. At the same time, the digital body of medical knowledge is growing exponentially. CDS is the key to enabling effective use of all of this information for the benefit of patients. It is an innovative tool that has the potential to drastically enhance the quality of care and increase efficiencies in the delivery of such care – both of which are needed in the current healthcare environment.

The international community's view of SaMD and the regulatory approach taken by IMDRF's members is of great interest to the MRC and the CDS Coalition. In this letter, we offer our appreciation for some of the specific content the forum has developed, observe an area where we think the proposal could use some additional clarity, and then offer some additional factors IMDRF may wish to consider. As a road map, we have provided a brief outline of our comments below:

I. Accomplishments of the IMDRF Proposal
    a. use of examples to define regulatory lines
    b. addressing accessory status
II. Issues which we believe need additional clarity
    a. the distinction between the treatment of software which is standalone and software which transforms a general purpose article into a medical device
    b. the role of software which simply executes on a general purpose platform
III. Additional Factors for IMDRF to consider
    a. rules relating to accessory status and the categorization and regulation of accessories
    b. interoperability as it relates to SaMD given the natural integration of health information technology into larger systems
    c. CDS software and the deregulation of CDS software where the user is not substantially dependent on the software
    d. intended uses of SaMD and particularly novel uses of software for wellness vs. disease management
IV. Addressing non-regulated software
    a. the IMDRF's framework for SaMD needs to define the line below which software should not be regulated

Lastly, we conclude with an expression of our appreciation of the IMDRF's efforts and a suggestion regarding the IMDRF's process in developing a framework for SaMD.

I. What the IMDRF Proposal does well

We are truly appreciative of IMDRF and in particular the achievement that the IMDRF Proposal represents. Pulling together the varied views of regulators from across the world could not have been an easy task. While there is much that we like about the IMDRF Proposal, we would like to highlight two features in particular that we think are very important.

A. Use of Examples

First, the IMDRF Proposal includes numerous examples. While any policy document needs to expressly define any lines that need to be drawn, providing examples of HIT software that fall on either side of those lines helps the reader truly appreciate and understand the lines that are drawn. Indeed, as a general principle, we would submit that anywhere a single example is helpful, two examples are even more helpful. Why? Because two points define a line. With two examples, the reader can look at both and identify the common elements between them. Identifying those common elements helps to illustrate the line that has been drawn. A single example, on the other hand, creates an ambiguity in the mind of the reader with regard to what feature of the example is truly important. In addition, examples that fall within the gray area are extremely helpful. Understanding how IMDRF views SaMD examples that are not obviously on one side of the line or the other will provide further insight into which characteristics are determinative of SaMD risk classification. The bottom line is we appreciate examples in addition to seeing the line articulated and the more challenging the example is, the better.

A. Status of Accessories

Second, the IMDRF Proposal, and more particularly the first SaMD document that includes definitions, expressly address the accessory status.[1] This status is terribly important because a very large number of the regulatory issues that involve SaMD stem from the potential of such software to be deemed an accessory to another medical device. And in practice, the potential accessory status greatly impacts both the risk categorization as well as the controls that are imposed.

In the sections below, we offer comments to aid IMDRF in addressing additional issues which are important to the HIT industry. Indeed, one of our focuses is further refining and providing context to the accessory question. We hope IMDRF will see these comments as we do – constructive feedback which will aid the forum in its creation of a framework for SaMD.

[1] On December 9, 2013, IMDRF issued IMDRF/WG/N10FINAL:2013, Final version of "Standalone Medical Device Software: Key Definitions". Section 3.0 References of IMDRF/WG/N10FINAL:2013 mentions GHTF/SG1/N071:2012: Definitions of Terms Medical Device and In Vitro Diagnostic Medical Device. Section 4.0 of GHTF/SG1/N071:2012, page 5 of 6, defines accessory to a medical device and accessory to an IVD medical device.

II. Issues to clarify

A. Standalone software vs. software that transforms a general purpose article into a medical device

To start with a classic example, a general purpose petri dish is just that, a simple petri dish that is not a medical device. It is unregulated in its base state. But what happens if we incorporate a disease focused purpose into the petri dish's intended use? When a manufacturer takes that petri dish and fills it with a certain agar to market it as a specialized tool for incubating particular bacteria in order to diagnose a particular disease, the whole package becomes a regulated medical device. At that point, the petri dish is no longer a general purpose article because it is intended to be used solely as a specialized diagnostic tool. It is no longer a petri dish that could be used for a variety of scientific purposes. In this case, the petri dish would be either a component or an accessory of the finished medical device, depending how it is delivered to the customer.[2]

The example above is relevant to the characterization of SaMD in the IMDRF Proposal. Unfortunately, the IMDRF Proposal combines two distinct categories of software which should be distinct like the two scenarios involving petri dishes detailed in our example. It mixes:

1. Software that is independent of a platform, and in fact can be used on any number of platforms and is itself a medical device, alone, *with*
2. Software that when combined with other general purpose articles by the vendor becomes part of a total system, collectively a medical device that literally touches the patient, delivering therapy or conducting diagnosis.

We firmly believe that software under (1) and (2) involve completely different regulatory scenarios. The IMDRF's framework for SaMD should at least separate, if not exclude from the definition of SaMD, any software which transforms hardware into a medical device. For example, a mobile app that transforms a cell phone, including the built-in microphone, into an electronic stethoscope should be outside the scope of SaMD regulation or at least placed in a separate category within the document. The following are a few examples contained in the guidance document which we think should be separated or excluded because they trigger different regulatory issues:

1. The IMDRF Proposal classifies software intended to reduce tinnitus through music therapy as SaMD. We think that is out of scope for this document and should be removed. The music therapy software might reside on a general purpose computer, but it is driving a medical device, namely headphones or speakers that are delivering music therapy. In that case,

[2] Vendors always have strategic choices in this regard. For example, an agar manufacturer could choose to simply sell its agar to customers and make specialized claims about the suitability the agar, and then advise its customers to go out and buy a petri dish that meets certain general specifications, dictated by whatever would be required for the safe and effective operation of the test. If, on the other hand, the vendor decides that from a business standpoint it can produce greater value by selling the fully configured agar plus petri dish, the vendor is taking on the obligation to include the petri dish in its quality system. So exactly what gets included in the regulated medical device the vendor sells is to some extent in the vendor's control.

music is not mere information, but rather is having a direct therapeutic effect on a patient. Certainly the headphones are not a medical device when sold by the manufacturer of the headphones, but they become a medical device when joined to a system that is promoted for the clear purpose of delivering therapy directly to a patient.

2. The same would be true of software that uses a microphone to listen for sounds of interrupted breathing – during sleep apnea events – and sounds a short tone to rouse the sleeper just enough to limit the pause to an acceptable interval. That system uses both microphones and speakers to aid in the treatment of a disease, sleep apnea, and thereby converts those general purpose electronics into medical devices.

There are a few other examples peppered throughout the document of software that is not simply operating on a general computing platform, but rather turning sensors into medical devices in the hands of the vendor, which according to the definition of SaMD, the software cannot do. Those examples should be removed from this guidance and addressed in a document focused on software that converts general-purpose sensors into medical devices. It is confusing to blend the two substantially different regulatory concepts and doing so will lead to a lack of certainty within the HIT industry and the regulatory community.

We must acknowledge that perhaps the confusion stems from assumptions regarding how a vendor provides its software. Perhaps in these examples, IMDRF contemplates that the software would be sold independently, and the software vendor would merely specify in general terms the type of hardware that would be necessary. In that instance, it would be like and agar manufacturer selling agar to customers, and simply telling them to go out and buy their own petri dish; resulting in the petri dish not being regulated. If that is what IMDRF is talking about, then the IMDRF should explain that more clearly.

Software that transforms hardware into a medical device should also be dealt with separately because it raises special issues that need to be addressed. As we explain in Appendix A, which is our policy proposal with regard to accessories, we believe that a general purpose article should retain its unregulated status so long as that general purpose article remains general purpose. For example, if a general purpose cell phone is sold for a wide variety of communication computing needs, it would remain unregulated even if it comes preloaded with medical device software. That scenario is different from our petri dish hypothetical above where the petri dish combined with the agar became a single product solely marketed for a specific medical use. The general purpose article would be promoted for general purposes, but obviously would include the specific medical purpose.

To return to some of the examples contained in the IMDRF Proposal, if the music for treating tinnitus is just sold like any music and could be played on any sound system, then the media containing the music alone would be the regulated article, not the numerous possible playback devices for that music. However, the analysis changes if the music is combined with some sort of computing device and headset into a dedicated unit used only for treating tinnitus. In that case, the software, computing device and headset form a dedicated system in the hands of the vendor that would be regulated as a medical device.

Our point is simply that the issues are different when the software has to be examined in the context of its relationship to certain hardware that actually delivers therapy or provides a diagnosis. Those issues should be dealt with separately to prevent inappropriate regulation of such software-hardware systems and also reduce ambiguity in the proposed framework for the regulation of SaMD.

B. Clarifying the criterion: the role the software plays

Based on the immediately preceding comment, in this section we focus on software that simply executes on a general purpose computing platform. The software does not directly deliver therapy to a patient, nor does it directly perform a diagnostic test or procedure. In our view, such software could receive data from a medical device, but it should not drive the medical device from which it is receiving data. In this section of our comment letter we are focused on a sub-set of this type of software which would function as CDS software and how it fits into the three-tier framework in the IMDRF Proposal.

Unfortunately, the distinctions between the three roles for software to play under the proposed document are difficult to understand. Before we get into the specific ambiguity, please allow us to state a few beliefs to ensure that they are accurate:

1. We believe that as presently defined, SaMD will never directly control the medical device, but rather will only communicate information to a human for that human agent to then make a decision on next steps. The definition of SaMD in section 5.1 of the December definitions document is a bit ambiguous on this point because it merely observes that the software will not be part of medical device hardware or drive medical devices.[3] The definition nonetheless contemplates that the software would interface with medical devices, which we interpret to mean largely receiving information from medical devices. We assume that SaMD would never be part of the closed loop system where the software might take in sensor data and then automatically make a decision which is communicated to a therapeutic medical device.

2. Another basic assumption here is that the introduction of SaMD does not result in a physician or other user receiving less information than he or she previously would have. One of the examples of SaMD is software that monitors a combination of ventilator data and patient monitor respiratory system signals to determine if breathing assistance is needed and advises either specific changes to ventilator settings or commencement of resuscitation efforts, as appropriate. We assume in that instance that the SaMD is in addition to the hardware and software that the anesthesiologist is presently using and all of the alarms that are presently available would remain available after the SaMD is incorporated. Thus we assume in this situation that the software is not configured to replace other information, but rather to supplement it.

[3] See note 1 above

3. While human beings have varying degrees of education and experience relevant to a particular issue, humans will always have some knowledge that they will bring to bear on the decision at issue. Thus, we would never simply ignore the role of the human in the equation.

4. We believe the document is focused on the intended use of the software, as opposed, for example, to the actual use of the software. Thus, in evaluating how the software should be categorized, the regulatory agency would focus on evidence of what the seller intends its customers to use the software for. That would certainly include labeling and promotional practices among other things. But it would not be based, for example, on some sort of surveillance with regard to how customers are actually using the software.

So in light of all that, if those assumptions are true, we are troubled by the categorization of software in the IMDRF Proposal based on whether the software would be a sole determinant of a diagnosis or treatment. How could SaMD ever be a sole determinant if it relies on human agency?

Let us put a finer point on that. As you well know, intended use statements are carefully crafted, oftentimes by a team that includes an attorney. In the normal course, an attorney would naturally make sure that the intended use statement carefully states that the software merely provides information based on inputs that the user of the software should carefully consider the information inputted, and ultimately use his or her own medical knowledge as well as more broadly consider other factors in coming to a decision. This kind of intended use statement is not only accurate, but necessary in a world where software manufacturers could find themselves in litigation should a patient get hurt. We would imagine the following as the typical scenario - (i) if SaMD is categorized based on intended use, and (ii) any SaMD that includes an intended use as a sole determinant in either treatment or diagnosis gets more highly regulated, then (iii) no software will claim to be the sole determinant of any diagnosis or treatment.

Based on the explanation above, if we understand the scope of this category of SaMD where it is the sole determinant of either diagnosis or treatment, we would predict that no software will fall into that category. That is the source of our confusion, because we assume that IMDRF believes that some software would in fact end up in this category. Unfortunately we cannot see how or why that would occur.

To be a little bit more specific, the IMDRF Proposal gives an example of radiation treatment planning software. In practice, radiation treatment planning software is never the sole determinant of a patient's treatment plan. If that were the case, the software could be used by an attorney (we want to pick as an example someone who is incredibly ignorant about medicine) to determine the treatment. That is clearly not the intent of the software and physicians everywhere would be rightly horrified if it was. If the planning software is to be used in connection with the treatment of cancer, the software can only be used by a radiation oncologist. A radiation oncologist is the appropriate end user for such software because we expect the oncologist to use his or her significant education, training and experience to decide what is right for each individual patient, and not just rely on the output of the software. Not only

is that true in reality, but we suspect that the labeling for these products universally explains that the user is supposed to bring his or her own judgment to the equation, and not automatically accept the output of the software. Even if that is not true now because of concerns over product liability and the desire to be fully informative to the user, it certainly would be true if this regulatory paradigm were adopted.

The same is true to a lesser extent of the other two categories, namely SaMD that drives clinical management or informs clinical management. If these regulatory categories are adopted, we predict that you will see labeling that declares that the information provided is merely to inform, and not to drive clinical management. We really struggled to understand the difference between driving and informing. To us it seems overly focused on the particular words of the software manufacturer uses it in its intended use statement, words that can be carefully chosen to achieve the desired categorization. In section 6.3, the IMDRF Proposal uses the phrase "SaMD that supplies information which is used as an aid in treating or diagnosing or in screening" a disease. In our view, virtually all relevant information provided in a very real sense aids in the treatment or diagnosis of a disease. In contrast, section 6.4 covers "software as a medical device and supplies information which is used in preventing/mitigating" the condition or "to supplement clinical management." To us the two categories are not truly distinct and both boil down to using information to make clinical decisions. In other words, there are not two objectively different uses here.

We made an earnest effort to carefully parse the language of IMDRF Proposal, but we fundamentally are having trouble understanding different roles for SaMD to play that cannot be substantially eliminated by careful wording of an intended use statement. This is unfortunately the case even though the guidance bases its distinction on a conceptual difference that is pretty fine to begin with. We think everything here will simply converge on the lowest category.

III. Additional factors for IMDRF to consider

While the current draft of IMDRF document reflects an enormous amount of thought by the IMDRF, we submit that there are a few other important issues that need to be addressed. Indeed, as we have informally observed during the IMDRF's process for crafting this document, it seemed as though the forum initially considered a wide variety of factors in prior drafts but then narrowed those factors substantially in producing the March 2014 draft. We are curious as to why IMDRF felt a need to narrow its focus? The following are some of the important topics that we would very much like to see addressed in the final version of this document.

A. The rules around accessory status

Above, in Section II.A of this commentary, we propose that IMDRF separate its discussion of (i) hardware/software combinations that can produce new medical device systems, from (ii) standalone software that merely executes, by itself, on a general purpose computing platform. Separating those topics will allow IMDRF to come up with clear guidance around the accessory status issue.

In this area, many medical devices are the product of hardware and software being stitched together into systems. Consequently, it is very important to come up with a framework for understanding the regulatory categorization of each component and the controls that apply. In the document attached as Appendix A, we outline some of these categorization issues that arise with connected hardware and software.

B. Interoperability

Interoperability is a universal characteristic of all software in the health information technology space. Unfortunately, the IMDRF Proposal does not address interoperability. We believe that this is a critical omission. Interoperability plays a critical role in health information technology systems and is an important safety consideration and factor in assessing risk of SaMD. Any SaMD will be a part of a larger system as a result of how the industry operates and the nature of SaMD itself. We urge IMDRF to address this issue in the IMDRF's framework for SaMD or identify how IMDRF plans to address the interoperability issue in the near future.

C. Substantial dependence on clinical decision support software

Again, as recommended in Section II.A, we propose separating out what would amount to CDS software from software that functions as an accessory or transforms a hardware/software system into a medical device. If IMDRF chooses to treat CDS software separately, we recommend that in addition to the seriousness of the disease and the role of the software (i.e. the type of recommendation made), that IMDRF consider whether the user is substantially dependent on the CDS.

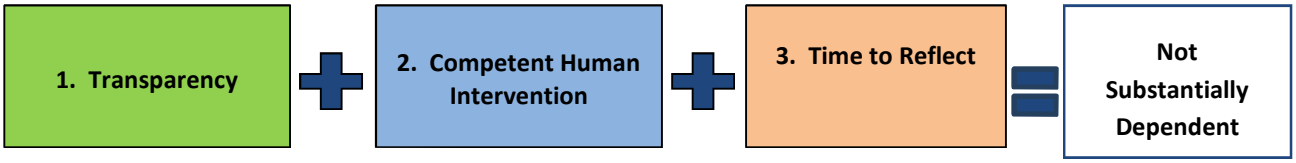
CDS software is different from a traditional medical device in that, as its name suggests, it supports the clinical decision made by healthcare professionals, patients, or users; it does not replace it. Traditional medical devices have a direct impact on the human body, or, in the case of diagnostic tests kits, they

analyze samples from the human body to derive information. CDS on the other hand only analyzes information, thereby facilitating the user's clinical decision making. Below, we briefly explain our view on how CDS should be regulated within a SaMD framework.

Our key premise is as follows: If the intended user is not substantially dependent on the CDS to make a diagnosis or treatment decision, a malfunction or error of that CDS will present little risk to the patient.

As a result, the CDS Coalition has developed a model that focuses on whether the user is substantially dependent on the CDS in making a diagnosis or treatment decision. CDS software that does not involve substantial user dependence should not be regulated.

The analysis of three criteria can determine whether the intended user is substantially dependent.



The Transparency criterion focuses on the features of software, its instructions for use, etc., and Competent Human Intervention and Time to Reflect criteria focus on the circumstances of the user.

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 contemplates disclosure of the following information:

    a. The information inputs used by the software. This includes (i) patient specific information which either the user can manually enter or the software can automatically pull from another source such as an Electronic Health Record, and (ii) the clinical information such as practice or professional guidelines that the software uses to analyze the patient information.

    b. The output or recommendation(s), and any applicable ranking and confidence levels.

    c. The clinical rationale for the recommendations and rankings. The software explains how it arrived at its recommendation based on the patient specific information and on the clinical guidelines or other tools the software used to process that patient specific information

If the software enables the intended user to determine how and why the recommendations are reached, the user would not be substantially dependent.

2. **Competent Human Intervention**. Is the intended user competent – through training, professional experience or otherwise – to make the clinical decision in question? The competent intervention depends on the ability and training of the user, and the nature of the decision. Thus, a patient, primary care physician, and a specialist are each competent to make different types of decisions.

If the software is intended to be used to support a decision the user is qualified to make without the use of the software, the user would not be substantially dependent. Conversely, software intended to be used to extend a user's decision making ability beyond his/her abilities would create substantial dependence.

3. **Sufficient Time to Reflect**. Is the user expected to have enough time to reflect on the software recommendation before making the decision? The amount of time available to reflect will depend on the acuity of the condition, or how much time can lapse before the patient receives medical care without risk to the patient. The amount of time needed to reflect will depend on the complexity of the decision.

If the intended user has time to appropriately consider the software recommendation (e.g., the time to determine the how and why of it, examine the patient directly, look at other diagnostic tools, etc.), the user would not be substantially dependent.

These criteria taken together assist vendors of CDS in determining whether the intended user is substantially dependent on their product, and thus whether their product would present material risk to patient and would be regulated. We humbly request IMDRF to carefully consider our proposed framework for the subset of SaMD that is CDS and consider incorporating the substantial dependence analysis into its final guidance.

D. Treatment of intended uses

One of the tricky aspects of dealing with SaMD is the really wide and growing number of intended uses. The existing IMDRF Proposal addresses many of the traditional intended uses, those that are highly focused on treating disease. One of the more difficult aspects of devising a regulatory framework for SaMD is addressing the growing, diverse number of intended uses that are focused on general wellness.

This is a big issue in the United States, and we have developed a policy proposal for how to differentiate intended uses that span from prescription devices used by patients, to those that should be available over-the-counter, and even those that should not be regulated because they involve general wellness. We submit the attached Appendix B that describes an approach to parsing these intended uses that we think would be useful for the IMDRF.

IV. What about software which should not be regulated at all?

If we understand IMDRF's intent correctly, the IMDRF Proposal was drafted to identify the risk factors that should be used in categorizing SaMD from highly regulated to lowly regulated. What is conspicuous by its absence is the concept of extending the risk-based framework down to software that should not be regulated at all.

On the one hand, we understand quite well that the scope of what gets regulated is defined by national law. In the United States, for example, the question is whether an article meets the definition of a medical device. But that hardly makes it a different issue than the categorization issue which IMDRF has clearly tackled. For example, US statutory law and not international norms dictate the meaning of class I, II and III. So the mere fact that the determination of regulated vs. non-regulated is a matter of national law is hardly a sufficient reason for distinguishing that issue from the categorization one.

It is our understanding that most jurisdictions take a practical approach to deciding what to regulate. They certainly start with a statutory definition of the regulated category – in the United States, the words "medical device" – but from there they have enforcement discretion to decide exactly what is worth regulating.

So we would encourage IMDRF to extend its analysis to the next logical step, which is discerning the risk line below which it is not worth regulating software as SaMD. To state the obvious, the document is not self-executing and each jurisdiction has to develop its own guidance or rules. So whatever IMDRF develops, it will not automatically become governing law anywhere. But the exercise of specifying the lower limit for regulation based on risk is a valuable one for both regulators and industry alike. It helps provide context and frame the discussion of risk on the lower limit and frankly adds credibility to the document because it shows the practicality of the concepts.

V. Conclusion

We apologize for the lack of line by line commentary as was technically requested by IMDRF. We did not provide line by line comments because that is quite honestly not where we had ideas and suggestions to express.[4] For the most part, we really like what is written, but we are suggesting some changes at a high level.

In this area of SaMD, there is an unusual situation where the international community is in many ways ahead of the national bodies. The forum is developing principles before national governing bodies are publishing their own guidance on the same topic. We think *that is a good thing* because it means that there should be a higher degree of harmonization than the norm where the international community trails national authorities.

If we could be bold for a moment, we would like to suggest a modified approach to IMDRF's process. In some ways, the IMDRF Proposal suffers from a level of detail that exceeds our current understanding with regard to how to regulate SaMD. The guidance is actually extraordinarily detailed and intricate on a few issues, but regrettably leaves out some key concerns. IMDRF has tried to engineer a detailed process and maybe even an action plan for national bodies, but at the cost of scope. In other words, we have achieved detail at the sacrifice of breadth.

This approach has led to a work product which is more akin to an algorithm rather than a narrative document. When a topic is susceptible of a formula, formulas are great because they are very precise. But where topics such as this one are so early in their development that the formulas are not discernible, trying to force the concept into a formula causes problems. And in this case, the problems are the big topics that are omitted.

This is a rare recommendation for us, but we recommend that IMDRF move away from a detail driven algorithmic approach and instead draft what might turn out to be a shorter document, but one that is simpler and more comprehensive. We think the issues included above are very important for the document. Some aspects of a SaMD framework may lend themselves to detailed explanation, but we firmly believe that general principles are more appropriate overall. This is particularly true due to the international nature of IMDRF. Guiding principles will be much easier to harmonize to varied national law and provide the flexibility needed to encourage adoption of a final framework for SaMD.

Please understand that our primary objective with this commentary is to assist IMDRF and address the needs of the HIT industry overall. We offer the critiques above to reach that objective, but are deeply appreciative of IMDRF's efforts and again applaud the forum for the IMDRF Proposal's achievements.

[4] As one small comment, under section 3.2, on page 6 of 25, in line 107 you use the word serious to define a critical condition. The problem is that the very next category, 3.3, is entitled serious conditions. We urge the IMDRF to consider further differentiating what is critical to distinguish it from what is merely serious through the use of more varied language.

If you have any questions or would like to discuss any of our recommendations, please do not hesitate to reach out to us.

Very truly yours,

Bradley Merrill Thompson

On Behalf of the mHealth Regulatory Coalition
and the Clinical Decision Support Coalition

Appendix A

Accessory Policy Proposal

We strongly believe that a nuanced approach is required for software that may become subject to regulation as an accessory to a regulated device. This policy outlines the MRC and CDS Coalitions' proposal regarding the definition and regulation of an accessory in the current environment of complex systems and interoperable products.

I. General Approach to Accessories

We propose the following approach to potential accessories.

A potential accessory will become an actual accessory regulated in the same class as the parent regulated medical device when the following three criteria are met:

1. The intended use – as demonstrated by words and deeds (for example by promotion and design) – of the potential accessory specifically includes use together with either:

    a. a specific branded medical device or

    b. a generic category of medical device.

    Automatic data transfer between software and devices associated with it is not required. Manual data entry can still occur as a part of the system intended to be used together.

2. The potential accessory is distributed to the end user without being integrated into the parent device and is "suitable for use or capable of functioning." (A product that does not meet this criterion might instead be a component); and

3. The relationship between the potential accessory and parent medical device is such that the potential accessory:

    a. Is necessary for the parent medical device to meet its intended use

    b. Augments or supplements the clinical performance of the parent medical device without changing the intended use of the parent medical device, **or**

    c. Is otherwise intended to affect the safety or effectiveness of the parent medical device.

If those three conditions are met, then the item is an accessory and is regulated. Despite being regulated, an accessory should not automatically be regulated in the same manner as the parent medical device, but should be classified based on the accessory's level of risk.

II. Medical device accessories do not cause general purpose hardware and software to be regulated

It is already clear that where software constitutes SaMD and is intended by the software manufacturer to be used with general purpose computing or communication hardware (such as a cell phone) or software (such as an operating system or standard communication protocols), the general purpose computing or communication hardware or software (sold separately by a separate manufacturer) is not a medical device. The same would be true when a specialized accessory that itself has medical device functionality (such as a blood glucose test strip reader) is intended to be used with a general purpose computing or communication product (sold separately by a separate manufacturer).

We propose that regulators go a step further and clarify that the general purpose hardware or software does not need to be sold separately by a separate manufacturer. Further, IMDRF should clarify that the general purpose computing or communication hardware or software remains unregulated even when the manufacturer of the general purpose hardware or software intends that the hardware is to be used with any suitable software, *and in its promotion specifically includes medical device software*. In other words, the fact that a general hardware or software company explicitly identifies a specific piece of medical software, among others, that can be used with its product should not cause the general article to become regulated. For example, a general purpose cell phone should remain unregulated even when it is specifically promoted for use with a medical device app, is sold preloaded with the medical device app or contains general purpose communication protocols that meet the needs of medical apps.

Of course, if the manufacturer of the general purpose computing or communications equipment adds specific hardware or software functionality that performs a medical device function and adds material risk, that functionality would be regulated. Taking a risk-based approach, there are functionalities that IMDRF should permit without regulation. For example, an app that retrieves, stores and forwards data, using standard communication protocols, from a medical device to a mobile medical app to enable the mobile medical app to apply algorithms to/manipulate the forwarded data for use in a non-acute situation.

III. Application of accessory rules to systems

One of the areas most in need of guidance is the application of the accessory rules to systems. Systems can be quite complex, such that an item might be an accessory to an accessory to an accessory of a medical device. We need some clarity from IMDRF regarding at which point that article no longer would be viewed as an accessory to the medical device.

We propose that each link in the system be examined using the approach outlined in section I of this Appendix, that is applying the five criteria to the article to see if it is an accessory *to an article that would be considered a freestanding medical device*. The analysis should always focus on the relationship between the potential accessory and the parent medical device. This is instead of considering whether an accessory somehow supports another accessory, which is too attenuated to declare a product regulated.

Further, the guidance should consider software modules or software add-ons to the parent software device. The IMDRF's framework for SaMD should also address system testing and the separation of modules/units that is required before such modules might be treated differently for regulatory purposes. It is typically difficult to draw regulatory lines between two connected software modules. In a separate position paper, we will recommend a specific approach to drawing lines between modules.

IV. Claims of interoperability

A claim that an accessory meets certain standards that are recognized as relevant to medical device functionality does not automatically mean the product is a regulated accessory. For example, the claim that an accessory is interoperable and/or compatible with a regulated medical device data management system type piece of software or hardware does not make the accessory any less of a general use item. Claims of interoperability and compatibility are commonly used to describe complex systems and underlying platforms. Because something is compatible or interoperable does not necessarily mean it has been optimized for use solely with medical devices and thus it can retain its general use status and should not be regulated. Only items of software or hardware that add material risk and make medical device claims should be regulated.

V. Regulatory requirements applicable to accessories

Regardless of the classification of an accessory, the following rules would apply to any intended use as an accessory.

1. Claims that certain products are compatible or interoperable with a medical device must be adequately substantiated and
2. The company making the claim must assure the claim remains accurate as the accessory or parent medical device changes over time.

So for accessories that are in fact regulated medical devices, instead of up classifying accessories, we recommend IMDRF recommend that regulatory bodies use their general authority (e.g., the Food and Drug Administration's authority under general controls in the US) to assure that companies are adequately validating accessory type claims. In other words, regulators should use their inspection powers to make sure that the validation has been done.

Appendix B

Parsing Intended Use – Wellness vs. Disease

We urge IMDRF to develop and issue a new guidance document explaining the difference between disease-related claims that would be regulated under a jurisdiction's medical device authorities, and wellness related claims that such jurisdiction may not regulate. This paper is intended to provide our proposed framework for such decision making.

I. Background: What is the issue?

In the old days, we lived under the fiction that taking care of health was dichotomous:

1. Doctors managed the diagnosis and treatment of disease and they did so largely in doctors' offices or hospitals.

2. Consumers generally understood that certain things like a well-rounded diet and exercise were good for us, and we managed that in our home by ourselves.

In that scenario a regulator's responsibilities were relatively clear. The regulators focused on the tools used by doctors in a healthcare setting to manage disease. For example, according to the 1976 Medical Device Amendments to the Federal Food, Drug and Cosmetic Act (section 201(h)), medical devices include those products "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals." The central thrust of that definition is that the product is used in connection with disease or other conditions, the word conditions being added to address such things as pregnancy. Thus, in the early days of the 1976 amendments, the definition was relatively clear in that it referred to products used in the domain of healthcare institutions to diagnose or treat disease or such conditions as pregnancy.

Today those activities are not so neatly separated. We have a much more sophisticated understanding with regard to how daily activities influence the likelihood of disease or other adverse health conditions. So consumers are taking proactive steps in their homes to better manage their health and ward off disease. Based on newly available genetic information, for example, consumers have a better understanding of where they may be at risk for disease, which in turn allows them to manage much more carefully the elements of their daily lives that constitute risk factors for that disease.

II. Old approach: assessing disease

The broad category of diagnostics was broken down into three subcategories.

Subcategory	Defining Characteristics Of The Subcategory
Screening	This is when a testing product is used on an asymptomatic patient with no indication that the patient has a given disease. At the same time, these products might be used on patients who are in some manner deemed higher risk of a disease, for example testing for hepatitis A among those who are sexually active. If a screening test produces a positive result, the patient is referred for diagnosis.
Diagnosis	This is when a testing product is used on a symptomatic patient to assess and confirm a diagnosis. So these products might be used, for example, when an adult presents an emergency room with pain radiating down both arms to confirm a myocardial infarction. If a patient is diagnosed with a certain disease or condition, depending on the disease, the physician may need to monitor that disease.
Monitoring	This is when a testing product is used on a patient who has a confirmed diagnosis, for the purpose of managing treatment over time. A common monitoring function is a blood glucose reader used to manage blood glucose levels for a patient with diabetes. One of the differences between this category and the other two is that this category of testing is done repeatedly over time as a part of management, where the other two are done at discrete points in time to inform a specific decision.

III. New approach: managing wellness

To that list of subcategories we propose to add the following 4th subcategory based on our understanding of modern trends in wellness management.

Managing wellness	This new category combines elements of screening and monitoring. • Like screening, these testing products would be used on asymptomatic patients where there may be some indication that the patient is at risk, for example because of family history, genetic makeup and other risk factors. • But like monitoring, instead of the one-time test, these tests would involve tracking clinical information over time to inform long-term health management. This is much akin to regular use of a weight scale when dieting.

IV. Emerging clinical evidence

There is a growing body of clinical evidence around preventive health and a consumer's ability to effectively ward off disease by better general health management based on information collected over time. That research focuses on areas such as the following:

Use case 1. Reducing the risk of diabetes.

- Target consumer: A person at risk of diabetes because of family history and weight. But presently the person does not have the symptoms of diabetes.
- The Center for Disease Control in the United States observes that people with prediabetes who lose 5%–7% of body weight and get at least 150 minutes a week of moderate physical activity can reduce the risk of developing type 2 diabetes by 58%.
- Product – an app that helps at risk persons manage their calorie intake, exercise level, and other factors known to reduce the risk of diabetes.

Use case 2. Reducing the risk of heart disease.

- Target consumer: A person at risk of heart disease because of family history, sedentary lifestyle, smoking and poor eating habits. But presently the person does not have the symptoms of heart disease.
- The American Heart Association (AHA) recommends a diet low in fat, particularly saturated and trans fats, enriched in fruits, vegetables, whole grains, and fish, and low in added sugar and salt.

The AHA also recommends against smoking. Smoking cessation may have beneficial effects on the lipid profile by increasing HDL-C (mean, 4 mg/dL). Exercise, physical activity, and weight loss may also increase HDL-C and lower triglyceride levels. The AHA recommends 30 minutes of moderate-intensity aerobic exercise on most days of the week.

- Product: an app designed specifically to track the elements of dietary intake related to the risk of heart disease, particularly fat and cholesterol levels. The app could also help implement elements of a smoking cessation program, and track physical activity, for example, by connecting to a pedometer.

The bottom line is that we as a society need to be encouraging use of products that help people live healthier lives. More to the point these apps do not engender any material risk, and therefore should not be excluded from classification as regulated devices in the IMDRF's framework for SaMD even though they mention disease.

V. Scope: What are the defining characteristics of products in this category?

In each of the three categories below, we are focusing solely on products used by consumers outside of a healthcare institution to measure information about their bodies. These categories include any specialized software or hardware, or combination of the two that serve these purposes.

Group A – Doctor- Directed Disease Assessment Devices

The essence of this category is devices designed to produce information that doctors are trained to interpret and understand, and consumers are not, but that are destined for consumer hands with the goal of feeding the information back to the doctor on some periodic basis. Devices in this category are easy to spot because there are existing device classifications in some jurisdictions for the associated functionality, such as urine analysis for occult blood and so forth. The common thread that runs through all of these measuring devices is well-recognized disease states or conditions associated with the information measured. Further, the devices will likely only be available through prescription in some jurisdictions because it will be necessary to involve a doctor in the interpretation of the information.

Obviously if devices are intended for use by doctors on patients, they too will be in this category.

Regulators generally regulate this category. For example, in the US many devices in this category will be in class II (i.e., higher risk), but some devices will be regulated as class I devices (or class II exempt, i.e., lower risk) because the technology is so well characterized that regulatory review is not necessary.

Group B – Consumer-Directed Disease Assessment Devices

The defining characteristic of devices in this category is that consumers are fully capable of interpreting the information produced by these devices, but at the same time the labeling makes specific claims that the product can be used to assess disease. It is important to understand that there can be a natural evolution of disease assessment tests from physician-directed to consumer-directed as companies innovate with new ways to make the information more meaningful to people without a medical

background. So long as the information is truly understandable by consumers without special medical training, assessing disease can include:

1. Screening
2. Diagnosis
3. Monitoring

Regulators should regulate the tools used for measuring in this category, and any associated accessories (see Appendix A above on the scope of accessory classification). Most of these devices should be regulated as low risk medical devices not subject to regulatory review, except those new technologies that are not well enough characterized to produce reliable results, where inaccurate results could substantially jeopardize the safety of the consumer. This latter category should be regulated at a higher risk level.

If a product is not a tool used for measuring, nor an accessory of such a product, the product should not be regulated. Examples of this would include mobile apps and other software that are merely intended to record and analyze health data for consumers.

Group C – Wellness Managing Devices

The defining characteristics of devices in this category are:

1. An intended use by consumers who
    a. are experiencing no meaningful symptoms of the disease at issue,
    b. but may or may not have risk factors of concern, including family history or genetic makeup
2. Repeated use over time for the purpose of tracking and trending health information
3. For the purpose of influencing lifestyle decisions to reduce the future risk of disease or other conditions, and
4. That do not present a safety risk because they are not invasive

The essence of this category is disease avoidance. So long as those four conditions are met, it is permissible for the labeling for these products to mention the diseases the products are intended to help the consumer avoid without triggering regulation.

We recommend the IMDRF's framework for SaMD indicate that regulators should not regulate this category.