IMDRF SaMD WG Comment Form	Date: 29 April 2024	Document: **Medical Device Software Considerations for Device and Risk Characterization**

Name/Organization	Line number	Section	Comments	Proposed change	Resolution
European Federation of Pharmaceutical Industries and Associations (EFPIA)					
EFPIA	Thematic	Thematic	We recognise that N81 will further the cause of harmonised interpretation of SaMD risk classification. We ask the IMDRF SWWG to emphasise that N81 is a companion document to N12 and not a replacement for key concepts such as the four-box classification system. There appears to be widespread confusion on this point already. The previous N12 guidance was not referenced in the Reference section and some of the initial concepts (e.g. SaMD characterization) were not mentioned in the current document.	Clarify that this new guidance is a companion document to the previous Guidance on risk characterization framework (IMDRF/SaMD WG/N12 FINAL:2014). Add N12 guidance in the references. Additionally, we would ask for further cross referencing to existing standards wherever possible.	
EFPIA	50-51	1 Introduction	There is a need to recognise that different stakeholders will require different kinds of information in different ways.	"Stakeholders**, to differing extents,** (including manufacturers, regulators, healthcare providers, end-users, and patients) **will** need to…"	
EFPIA	85-112	2.2 Scope of the document	The scope of the document now includes medical device software, irrespective of the software technology or platform (including hardware medical device). More specific explanation of N12 likely required to clear up confusion, as some have interpreted N81 as a replacement for N12 and the four-box classification.	Suggestion to clarify how this document should be used in conjunction with N12 (as a companion). In particular e.g., how the SaMD categories from the N12 document align with the new risk characterizations in this draft N81 document. Addition of a new bullet in Section 2.2: **"This document is <u>not</u> intended to replace *IMDRF SaMD WG N12 "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations*. Rather, this document supplements and elaborates on the general risk categorization framework articulated in N12."**	
EFPIA	111 - 112	2.2 Scope of the document	¶*"The content in this document is not regulation and does not imply a convergence of regulations or categorization rules across jurisdictions. Additional work may be required to apply*	Recommend including the following additional statement after line 112, "**However, this document aims to establish harmonized concepts, considerations, and common vocabulary for the risk characterization of**	

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			and align these concepts in a given jurisdiction". The mission of the International Medical Device Regulators Forum is to strategically accelerate international medical device regulatory convergence to promote an efficient and effective regulatory model for medical devices that is responsive to emerging challenges in the sector while protecting and maximizing public health and safety. As noted in the document, this guidance is not regulation and does not imply a convergence of regulations or categorization of rules across jurisdictions, however, it is important to clarify that the intent of these IMDRF documents is to facilitate timely access to safe medical devices for patients through harmonized and aligned guidance on appropriate regulatory controls for medical device software.	**medical device software**."	
EFPIA	188-191	4.1.1. Key Elements of Intended Use/Intended Purpose Statement	¶*"7. Medical device software function, including:* • *Medical device software inputs* • *Medical device software outputs* • *Explanation of how the medical device software inputs and outputs fit into the clinical or healthcare workflow"* The associated interface (if applicable) must be considered part of the medical device "system" as it receives input and may provide output if the interfaces are bi-directional. They would also be aligned with data flow diagrams and architecture.	Add a 4th bullet point: • **Associated interfaces and inputs and outputs (if applicable)**	
EFPIA	193-196	4.2. Device Description - Medical	¶"*A detailed medical device software description, accompanying the intended use/purpose statement, is often needed to*	Add "**and associated data flow diagrams/architecture".**	

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		Device Software	*ensure the comprehensive and adequate communication of all necessary characteristics and information related to a medical device software"'.*	A detailed medical device software description, **and associated data flow diagrams/architecture**, accompanying the intended use/purpose statement, is often needed to ensure the comprehensive and adequate communication of all necessary characteristics and information related to a medical device software.	
EFPIA	203	4.2. Device Description - Medical Device Software	The guideline explains that change management is one of four elements relevant to the characterization of a medical device software. Change management or control is a software engineering discipline that ensures control with SaMD or SiMD configuration, including software, configuration parameters, infrastructure and data. Change management/control applies to any type of software, ref. ISO 90003:2018.	Further clarification is needed, highlighting that only machine learning/artificial intelligence capabilities may be different to other software with regards to change management in the risk characterization of medical device software.	
EFPIA	215-221	4.2.1. Medical Problem and/or objective	¶ *"A medical device may be used in different stages of the care pathway, such as diagnosis (e.g., primary diagnosis, screening, triage, staging, etc.); treatment (e.g., relieving symptoms or restoring function); prevention (e.g., averting the occurrence of a disease or condition); prediction (e.g., disease prognosis, anticipated treatment response, etc.) or monitoring (e.g., ongoing assessment of patient parameters)"* *nt response, etc.) or monitoring (e.g., ongoing assessment of patient parameters)"* We would like to remove the example of "anticipated treatment response" for prediction in the IMDRF N81 draft guidance as it goes beyond what is currently considered in local regulation such as the EU MDR.	Remove: "**anticipated treatment response**" "A medical device may be used in different stages of the care pathway, such as diagnosis (e.g., primary diagnosis, screening, triage, staging, etc.); treatment (e.g., relieving symptoms or restoring function); prevention (e.g., averting the occurrence of a disease or condition); prediction (e.g., disease prognosis, ~~anticipated treatment response~~) or monitoring (e.g., ongoing assessment of patient parameters)".	

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			The medical device definition in MDR states that a medical device can be software that generates info for the prediction of a disease. However, prediction of treatment effect is not included. Note: device definition in EU MDR: "...diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of the disease"		
EFPIA	272-274	4.2.2 context of MDSW use	It is suggested that the concept of 'weight' of the software's use should be specifically tied back to the manufacturer's intended weight rather than a description of use that may include off-label practices.	"These are important to understand the "weight" of the software's use **that the manufacturer intends** and can help to identify where and how effects from the software use can alter the course of a patient's healthcare experience."	
EFPIA	Table 2. Timing Within Healthcare Task/Intervention	4.2.2 context of MDSW use Early, midway, late	¶ *"Timing Within Healthcare Early (e.g., triage, prediction of future diagnoses, early investigations upon Task/Intervention"*	The timing within healthcare task/intervention needs to be more clearly defined because early, midway, and late timing phases are only described using examples. Also, the examples provided need to be further clarified. For example, it is unclear how "routine monitoring of patient health" would fall under midway timing of a healthcare task or intervention. Also, "autonomous detection and diagnosis of diabetic retinopathy" is given as an example of late timing within a healthcare task or intervention, but diabetic retinopathy has different stages of severity from very mild non proliferative diabetic retinopathy to advanced proliferative diabetic retinopathy.	
EFPIA	Table 2. Timing Within Healthcare Task/Intervention	4.2.2 context of MDSW use *Note	¶ "*Rather, it is important to characterize the timing of the output relative to the final intervention, decision, or action as well as the relative chronology of how the product will be introduced in relation to other steps (e.g., prior steps, concurrent steps, conditional steps, subsequent steps) and current standard medical practices."* This note is emphasizing the importance of characterizing the timing of the medical	Recommend revising the sentence to the following, "Rather, it is important to characterize the timing of the output relative to the ~~final~~ intervention, decision, or action **for the medical device software's intended use /purpose** ~~as well as the relative chronology of how the product will be introduced in relation to other steps (e.g., prior steps, concurrent steps, conditional steps, subsequent steps) and current standard medical practices~~".	

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			device software output relative to the final intervention, decision, or action as well as the relative chronology of how the product will be introduced in relation to other steps and current standard medical practices discusses considerations related to the practice of medicine. We consider this is out of scope and not appropriate for this type of document.		
EFPIA	279-345	4.2.3 MDSW function and/or use Degree of clinical autonomy	Although clinical autonomy is discussed in this document, it does not acknowledge or consider the importance of patient autonomy. The use of certain medical device software can empower patients with decision-making capacity to make certain decisions regarding their care.	Please include a discussion and consideration of patient autonomy in the context of medical device software risk characterization because the degree of patient autonomy can also inform the potential harms and benefits that a medical device software can introduce within a given context of use.	
EFPIA	308-317 (as well as related later references)	4.2.3. MDSW Function and/or Use	Reference to current state of the art and applicable standards to characterise levels of autonomy would likely be of assistance as this distinction seems too coarse to be future proofed. For instance, IEEE 7001, NIST SP 1011-II-1.0, IEEE Std 1872-2015.	Substantive revision around a commonly used set of levels of autonomy noted in comments and link to existing state of the art.	
EFPIA	315-317	4.2.3. MDSW Function and/or Use	¶*"Semi-automated outputs are made available for critical assessment and approval or editing and, finally, for manual outputs, the user controls the generation of the output. The level of automation is determined irrespective of whether the user is a clinical or non-clinical user".* It is not clear why semi-automated outputs are only intended to be assigned to "critical" assessments. The level of automation should be assigned irrespective of the criticality of the processed output.		
EFPIA	328-335	4.2.3. MDSW Function and/or Use	The document would benefit from distinguishing between concepts such as explainability and interpretability versus more general transparency. While	Insert**: A description of information related to transparency should be provided, this might include (but is not limited to): information about the model used (such as, deterministic**	

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			explainability and interpretability may be a part of overall transparency, often transparency that might include description of the training / tests sets, suffices versus the much more technically demanding explainability. The document should not confuse these concepts.	**formulae; machine learning approaches; mathematical simulations; etc.), key details about any test datasets used, and other information necessary for the user to safely operate the device. Manufacturers should also consider the human interpretability and explainability of their model and its relationship to the user and safety of the device."**	
EFPIA	329-332	4.2.3 Medical Device Software Function and/or Use	¶ *"This includes the information about the software algorithm or technology utilized (such as, deterministic formulae; machine learning approaches; mathematical simulations; etc.) and information about how an output or result was reached or the basis for a decision or action."* Additional guidance and common vocabulary for the level of intelligibility, transparency, and explain ability would be helpful for example, diversity of training set, mitigations to address bias, etc.	It is recommended to standardize the minimum information and feature attributes for algorithm intelligibility, transparency, and explain ability of the underlying logic.	
EFPIA	332-335	4.2.3. MDSW Function and/or Use	Apart from the different statuses suggested for explainability or comprehensibility, it is not entirely clear what the reference point is for these assessments. For instance, authors such as Guidotti (2018) often distinguish between global interpretability, that is, what the model generally finds significant versus local interpretability, that is, what the model found significant for a particular output. It is suggested that the document clarifies which kind of interpretability is meant here; it looks like the authors intend local interpretability to be reference point or both local and global. For more information see: Guidotti R, Monreale A, Ruggieri S, et al. A Survey of	Clarification of what the object of reference for explainability or comprehensibility is in this case.	

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			Methods for Explaining Black Box Models. ACM Computing Surveys. 2018; 51(5); 6.		
EFPIA	346-379	4.2.4 MDSW change management	The area covered in section 4.2.4 are so different, that change management of AI/ML performance, management of implemented software changes, management to software infrastructure, are quite different disciplines following different processes, techniques, tools etc.	Please consider explaining how change management listed in line 203 and detailed in section 4.2.4. contributes to the characterization of a medical device software per topic: - Change management of distribution channels - Change management of AI/ML - Change management of software and infrastructure changes This can be done in section 4.2.2 Context of MDSW use. An overall definition of the term “change management” would also be useful.	
EFPIA	347-349	4.2.4. MDSW change Management	¶ “*The change management approaches tied to a device form part of the device characterization, including the autonomy of learning or change implementation as well as the intended domain of change implementation.”* This guidance specifically lists learning capabilities, autonomy and management as an attribute that can impact SaMD risk characterization. While the other attributes clarified in the previous sections of the guidance can be translated into “Criticality of information” and “Target Health status” (the parameters of the IMDRF N12 Risk categorization table), it is not clear the link between learning capabilities and those parameters of the matrix.	Clarify the link between the learning capabilities (relevant for AI, and which the IMDRF N12 does not cover) and the risk characterization matrix of IMDRF N12 (category I to IV).	
EFPIA	352-355	4.2.4 MDSW change management	Question whether there are existing technical distinctions and references to state of the art that could be made instead of self-learning versus externally controlled learning to reference existing concepts and to be more precise. For instance, technical	Reformulation around existing technical distinctions and reference to existing state of the art wherever possible.	

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			terms such as 'continuous learning' or 'incremental learning' where streaming data is input versus 'batch learning' might be better used when contextualised within the document.		
EFPIA	356-358	4.2.4 MDSW change management	Query: how does the WG view 'calibration' with respect to training, learning, and updates? Is calibration just another species of change to be managed? It seems common to view some of the changes, especially some clinic-specific and patient-specific changes as calibration where these changes are designed for and included within the manufacturer's intended use/purpose.	N/A query.	
EFPIA	367-372	4.2.4. Medical Device Software Change Management	It is also unclear how Distribution channels are relevant to change management.	Examples may be useful.	
EFPIA	393-395	5. MDSW risk characterizatio n	¶ "*In other words, when assessing the risk of medical device software, it is important to understand the contribution of information-related hazardous situations, which are closely tied to the role of software'.*	Add **functionality** after the role of software ''In other words, when assessing the risk of medical device software, it is important to understand the contribution of information-related hazardous situations, which are closely tied to the role of software **functionality.''**	
EFPIA	401-404	5. MDSW risk characterizatio n	¶ *"An accurate characterization of software, including its characteristics such as intended use, output type, use environment, autonomy, etc., allows for both a more comprehensive identification of these direct and indirect harms and a clear understanding of how software-specific harms can then lead to risks unique to a given intended use/purpose."*	Add **functionality and specifications** after intended use. An accurate characterization of software, including its characteristics such as intended use, **functionality and specifications**, output type, use environment, autonomy, etc., allows for both a more comprehensive identification of these direct and indirect harms and a clear understanding of how software-specific harms can then lead to risks unique to a given intended use/purpose	
EFPIA	413-419	5. Medical	¶ "*Therefore, it can be helpful to consider*	Clarify the incorporation of cybersecurity risks	

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		Device Software Risk Characterization	*software-specific considerations pertaining to harm as a combination of how harm is defined for safety and cybersecurity. In other words, medical device software-specific consideration of harm could be viewed as relating to injury or damage to the health of people and reduction of effectiveness – where "reduction of effectiveness" can result from inadequate, incorrect, or absent data supplied to a human or product at an inappropriate time, rate, or with an inadequate method."* While cybersecurity is mentioned, no guidance is given to use cybersecurity risk management as an input to the device risk characterization.	when performing the device risk characterization.	
EFPIA	419-424	5. MDSW risk characterization	¶ "*For example, injection of unwanted or unintended bias into a decision-making system, whether or not it results in direct harm to a patient, can be understood as a harmful reduction in effectiveness. In other words, the introduction of the particular software solution has had a negative impact on the decision-making system. Often, this can also be viewed as accounting for "indirect harm" from the software, as noted above."*	Add "**with potential direct impact to the patient"** ''A human or product at an inappropriate time, rate, or with an inadequate method. For example, injection of unwanted or unintended bias into a decision-making system, whether or not it results in direct harm to a patient, can be understood as a harmful reduction in effectiveness. In other words, the introduction of the particular software solution has had a negative impact on the decision-making system. Often, this can also be viewed as accounting for "indirect harm" from the software, **with potential direct impact to the patient** as noted above**."**	
EFPIA	524-527	5.3 Approaches for risk categorization	The authors may wish to highlight that it is risk as identified prior to controls rather than residual risk (under 14971) that goes to risk classification in the context of N81 and N12 to ensure these two are not confused.	Insert, where appropriate: "**It is risk as assessed prior to risk controls (rather than residual risk) that is relevant for medical device software classification purposes under this document and N12."**	
EFPIA	521-530	5.3	It is not clear how the current risk	Clarification	

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	594-596	Approaches for risk categorization and Appendix B	considerations relate to the risk categories outlined in Section 7 of IMDRF/SaMD WG/N12FINAL:2014.		
EFPIA	594	Appendix B	*Intelligibility/Transparency/Explainability of Underlying Logic including the Algorithm/Technology used and How an Output is Reached*	It would be helpful for the AI-type characterisations, e.g. fully automated output, "Black box" to be dealt with in a separate section.	
EFPIA	594	Appendix C	*Intended Patient Population •Does the intended patient population include a specific vulnerable subgroup? •How diverse is the intended patient population? How generalized does the information need to be to perform adequately across the intended patient population? How specific? •Does the medical device software accurately reflect the demographics, backgrounds, and characteristics of the population the software will be used for?*	The data the software is basing the decision and output on should be mentioned. "'Does **the data the software is processing** accurately reflect the demographics, backgrounds, and characteristics of the population the software will be used for?"' Please address the lack of data when considering items like vulnerable groups that would point to bias as well.	
EFPIA	838	Appendix E	Make the link with IMDRF N12.	Include an appendix with examples on how the different attributes described in this document align with the SaMD categories from N12 (Categories I to IV).	

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