INTERNATIONAL TELECOMMUNICATION UNION

**TELECOMMUNICATION STANDARDIZATION SECTOR**

STUDY PERIOD 2017-2020

**FG-AI4H-M-052**

**ITU-T Focus Group on AI for Health**

**Original: English**

| | | |
|---|---|---|
| **WG(s):** | Plenary | Online, 28-30 September 2021 |

**DOCUMENT**

| | |
|---|---|
| **Source:** | Editors |
| **Title:** | DEL02 update: Overview of Regulatory Considerations on Artificial Intelligence for Health (Draft 3.3) |
| **Purpose:** | Discussion |


| | | |
|---|---|---|
| **Contact:** | Shada ALSALAMAH<br>WHO | E-mail: alsalamahs@who.int |
| **Contact:** | Khair ElZarrad<br>FDA, USA | E-mail: mohammed.elzarrad@fda.hhs.gov |
| **Contact:** | Rose Purcell<br>FDA, USA | E-mail: Rosemarie.Purcell@fda.hhs.gov |
| **Contact:** | Jackie Ma<br>Fraunhofer HHI, Germany | E-mail: jackie.ma@hhi.fraunhofer.de |
| **Contact:** | Sameer Pujari<br>WHO | E-mail: pujaris@who.int |


**Abstract:** This document contains the draft version 3.3 of the FG-AI4H Deliverable 2 Overview of Regulatory Considerations on Artificial Intelligence for Health. It is provided for review and feedback from the FG-AI4H members.

Feedback on this version of DEL2 is requested by 1 October 2021.

This document was submitted as M-052 at the FG-AI4H meeting M, online, 28-30 September 2021.

| Targeted Month | Planned Milestones/ Deliverables |
|---|---|
| **Sep** | • Receive reviewers' comments on DEL02 draft v3.3<br>• Present at FG AI4H Meeting M |
| **Oct** | • Create a new DEL02 draft v4.x with reviewers feedback addressed<br>• WHO Clearance<br>• FG Clearance |
| **Nov** | • Submit DEL02 draft v4.x to WHO editors with final recommendations |
| **Dec** | • Receive final approval from WG-RC contributors after an internal check with their organizations |

# Overview of Regulatory Considerations on Artificial Intelligence for Health

Working Group on Regulatory Considerations
on Artificial Intelligence for Health

*Edited Draft*
*v3.3*
*01/08/2021*

*NOT FOR CIRCULATION*

## Acknowledgements

Development of this guidance document was led by Sameer Pujari (Department of Digital Health and Innovation), under the overall guidance of Bernardo Mariano (Director, Digital Health and Innovation) and Soumya Swaminathan (Chief Scientist).

Shada Alsalamah (Department of Digital Health and Innovation) was the lead writer and subgroup lead of the Data Quality and Total Product Lifecycle Approach & Risk Management topic areas along with Judith Van Andel (Department of Digital Health and Innovation). The remaining topic areas were led by the following subgroup leads: Khair ElZarrad, (U.S. Food and Drug Administration, USA) led the Documentation & Transparency topic area; Monique Kuglitsch (Fraunhofer Institute for Telecommunications, Heinrich Hertz Institute, HHI, Germany) and Dean Ho (National University of Singapore, Singapore) jointly led the Engagement & Collaboration topic area; Naomi Lee (The Lancet, UK) led the Intended Use and Analytical & Clinical Validation topic area; and Rose Purcell (U.S. Food and Drug Administration, USA) led the Privacy and Data Protection topic area.

WHO is grateful to the following individuals who contributed to development of this publication:

**Subgroup technical experts**

Pat Baird (Philips, USA), Data Quality topic area subgroup technical expert.
Tim Kelsey (HIMSS, UK), Privacy and Data Protection and Documentation & Transparency topic areas subgroups technical expert.
Andrea Keyter (Key Largo Consulting Group, South Africa), Documentation & Transparency and Engagement & Collaboration topic areas subgroups technical expert.
Xiaoxuan Liu (University of Birmingham, UK), Intended Use and Analytical & Clinical Validation and Total Product Lifecycle Approach & Risk Management topic areas subgroups technical expert
Ugo Pagallo (University of Turin, Italy), Privacy and Data Protection and Engagement & Collaboration topic areas subgroups technical expert
Tayab Waseem (Stability.ai, USA), Total Product Lifecycle Approach & Risk Management topic area subgroup technical expert.

**External expert group**

Najeeb Al-Shorbaji, eHealth Development Association, Jordan
Fazilah Shaik Allaudin, Malaysian MoH, Malaysian
Abdulgader Almoeen, National Center for AI (NCAI), Saudi Data & AI Authority (SDAIA), Saudi Arabia
Michael Berensmann, Federal institute for drugs and medical devices (BfArM), Germany
Hélio Bomfim de Macêdo Filho, Anvisa, Brazil
Luca Foschini, Evidation Health, USA
GHAZAL Hassan, Moroccan Society for Telemedicine and eHealth, Morocco
Indra Joshi, NHSX, NHS, UK
Kassandra Karpathakis, NHSX, - NHS, UK
Vladimir Kutichev, Russian Federal Service for Surveillance in Healthcare, Russia
Marc Lamoureux, Health Canada, Canada
Tze-Yun Leong, National University of Singapore and AI Singapore, Singapore
Liang Hong, China's Center for Medical Device Evaluation (CMDE), China
Lin Anle, Health Sciences Authority, Singapore
Junaid Nabi, Harvard Medical School, USA
Mats Ohlson, Mats Ohlson MT-Advisor, Sweden
Adrian Pacheco-Lopez, CENETEC Ministry of Health, Mexico
Beatrice Panico, MHRA, UK
Andres Pichon-Riviere, Institute for Clinical Effectiveness and Health Policy - IECS, Argentina

Julie Polisena, Health Canada, Canada
Pierre Quartarolo, Danish Medicines Agency (DKMA), Denmark
Chandrashekar ranga, The Central Drugs Standard Control Organisation (CDSCO), India
Mansooreh Saniei, King's College London, UK
Raymond Francis R. Sarmiento, University of the Philippines Manila, Philippines
Kanako Sasaki, Ministry of Health, Labour and Welfare, Japan
Robin Seidel, BfArM, Germany
Rama Sethuraman, Health Sciences Authority, Singapore
Robert Ssekitoleko, Makerere University, Uganda
Bev Townsend, University of KwaZulu-Natal, South Africa
Georg Zimmermann, Paracelsus Medical University, Austria

**External reviewers**

Thomas Wiegand, Fraunhofer Heinrich Hertz Institute, Germany

**Observers**

Johner Christian, Johner-institut, Germany
Wolfgang Lauer, BfArM, Germany
Peng Liang, China's Center for Medical Device Evaluation, China
Dinsie Williams, Utoronto, Canada

**WHO staff**

Shada Alsalamah, Consultant, Digital Health and Innovation, Geneva
Adriana Velazquez Berumen, Digital Health and Innovation, Geneva
Wouter 'T Hoen, HR Officer, Geneva
Stephanie Yetunde Kuku, Consultant, Digital Health and Innovation, Geneva
Rohit Malpani, Consultant, Health Ethics and Governance Unit, Geneva
Bernardo Mariano, Chief Information Officer, Geneva
Sameer Pujari, Technical Officer, Digital Health and Innovation, Geneva
Andreas Reis, Co-Lead, Health Ethics and Governance Unit, Geneva
Soumya Swaminathan, Chief Scientist, Geneva
Mariam Shokralla, Consultant, Digital Health and Innovation, Geneva
Yu Zhao, Technical Officer, Digital Health and Innovation, Geneva

## Disclaimer

This publication reflects the listed contributors' personal views and perspectives that may not necessarily reflect the positions and opinions of their organizations. Furthermore, these considerations are not inclusive and regulatory bodies may have additional or different approaches.

## Executive Summary

The World Health Organization (WHO)'s mission to promote health, keep the world safe, and serve the vulnerable is articulated in its global strategy on digital health 2020–2025[1]. At the heart of this strategy, the WHO aims to improve health for everyone, everywhere by accelerating the development and adoption of appropriate, accessible, affordable, scalable and sustainable person-centric digital health solutions to prevent, detect and respond to epidemics and pandemics, developing infrastructure and applications. The WHO also recognizes the potential of Artificial Intelligence (AI) in enhancing health outcomes by improving medical diagnosis, digital therapeutics, clinical trials, self-management of care and person-centered care, as well as creating more evidence-based knowledge, skills and competence for professionals to support health care. Furthermore, with the increasing availability of healthcare data and the rapid progress of analytics techniques, AI has the potential to transform the health sector to meet a variety of stakeholders' needs in healthcare and therapeutic development.

In order to facilitate the safe and appropriate development and use of AI solutions in healthcare, the International Telecommunication Union (ITU) and the WHO established a Focus Group on AI for Health (FG-AI4H). To support its work, FG-AI4H created a Working Group on Regulatory Considerations (WG-RC) on AI for Health. The WG-RC consists of members representing multiple stakeholders including regulatory bodies, policy makers, academia, and industry who explored regulatory and health technology assessment considerations and emerging "good practices" for the development and use of AI in healthcare and therapeutic development. The work of the WG-RC represents a multi-disciplinary, international effort to increase dialogue and examine key considerations for the use of AI in healthcare.

This publication, which is based on the work of the WG-RC, aims to deliver an Overview of Regulatory Considerations on Artificial Intelligence for Health that covers the following six general topic areas: Documentation & Transparency, Total Product Lifecycle Approach & Risk Management, Intended Use and Analytical & Clinical Validation, Privacy and Data Protection, and Engagement & Collaboration. This overview is not intended as a guidance, as a regulatory framework, or policy. Rather, it is a discussion of key regulatory concepts and a resource that can be considered by all relevant stakeholders in medical devices ecosystems, including but not limited to, developers who are exploring and developing AI solutions, regulators who might be in the process of identifying approaches to manage and facilitate AI solutions, manufacturers who design and develop AI-embedded medical devices, and health practitioners who deploy and use such medical devices and AI solutions. Consequently, the WG-RC recommends that stakeholders take into account the following considerations as they continue to develop frameworks and best practices for the use of AI in healthcare and therapeutic development:

1. *Documentation and Transparency:* Pre-specifying and documenting the intended purpose and development process, such as the selection and use of datasets, parameters, metrics, deviations from original plans, and updates, during the phases of development should be considered in a manner that allows for the tracing of the development steps as appropriate. A risk-based approach should be considered for the level of documentation and record keeping utilized for the development and validation of AI solutions.
2. *Total Product Lifecycle Approach and Risk Management:* A holistic risk management approach that addresses risks associated with an AI medical device, such as cybersecurity threats and vulnerabilities, should be considered throughout all phases in the life of a medical device and the key broad management categories: pre-market development management, post-market management, and change management.

[1] Global Strategy on Digital Health 2020– 2025. Geneva: World Health Organization; (2020) (https://www.who.int/docs/default-source/documents/gs4dhdaa2a9f352b0445bafbc79ca799dce4d.pdf?sfvrsn=f112ede5_58)

3. *Intended Use, and Analytical and Clinical Validation*: Transparent documentation of the intended use of a tool including the setting and patient should be provided. Details of the training dataset composition underpinning an AI tool, including size, setting and population, input and output data and demographic composition should be transparently documented and provided to users. External analytical validation in an independent dataset is required to demonstrate performance beyond the training data. This should be representative of the population and setting in which the tool is intended to be deployed, and transparent documentation of the external dataset and performance metrics should be provided. For clinical validation, a graded set of requirements based on risk is recommended. Randomized clinical trials are the gold standard for evaluation of comparative clinical performance and could be appropriate for the highest risk tools or where the highest standard of evidence is required. Prospective validation is real world deployment and implementation trial which a relevant comparison group showing a meaningful improvement in outcomes using accepted endpoints may be appropriate for other risk classes. A period of more intense post-deployment monitoring for adverse events should be considered. Further consideration of this is being undertaken by the WG on clinical evaluation.
4. *Data Quality:* Developers should determine if available data is of sufficient quality to support the development of systems that can achieve their intended goal. Furthermore, developers should consider deploying rigorous pre-release trials for AI solutions to ensure that they will not amplify any of the issues, such as biases and errors due to any issues with the training data, algorithms, or other elements of system design. Moreover, careful design or prompt troubleshooting can help identify data quality issues early on. This could potentially prevent or ameliorate possible resulting harm. Finally, to mitigate data quality issues that arise in healthcare data and the associated risks, stakeholders should continue to work to create data ecosystems to facilitate the sharing of good-quality data sources.
5. *Privacy and Data Protection:* Privacy and data protection should be considered during the design and deployment of AI solutions. Early in the development process, developers should gain an understanding of applicable data protection regulations and privacy laws and ensure the development process meets or exceeds such legal requirements. A compliance program should address risks and develop privacy and cybersecurity practices and priorities that take into account potential harm, as well as the enforcement environment.
6. *Engagement and Collaboration:* It is important to consider the development of accessible and informative platforms that facilitate engagement and collaboration, where applicable and appropriate, among key stakeholders of the AI innovation and deployment roadmap. These include and are not limited to AI/ML developers, device manufacturers, healthcare practitioners, policymakers, and regulatory bodies. These engagement and collaboration platforms may play a key role in streamlining the oversight process for AI regulation while also accelerating practice-changing advances in AI to the user community.

Finally, the WG-RC has provided a forum for regulators and subject matter experts to discuss regulatory considerations for the use of AI in healthcare and therapeutic development. The WG-RC recognizes that the AI landscape is rapidly evolving and that the considerations in this deliverable may require expansion as the technology and its uses develop. It recommends that stakeholders, including regulators and developers, continue to engage and that the community at large works towards shared understanding and mutual learning. In addition, established national and international groups, such as the International Medical Device Regulators Forum (IMDRF) and International Council for Harmonization of Technical Requirements for Pharmaceutical for Human Use (ICH), should consider the topic of AI for potential standardization (where useful) and for harmonization efforts in general.

**Commented [MR1]:** I think standardisation makes sense so that all countries (and developers) work from a common language. Yet harmonization - while it can be convenient for developers and perhaps regulators - can also be profoundly undemocratic. Countries may want to set different regulatory standards, and often tougher standards, depending on the challenges they face and the concerns expressed by their own populations towards the use of certain technologies.

# Table of Contents

# 1. Introduction

The World Health Organization (WHO)'s mission to promote health, keep the world safe, and serve the vulnerable is articulated in its global strategy on digital health 2020–2025[2]. At the heart of this strategy, the WHO aims to improve health for everyone, everywhere by accelerating the development and adoption of appropriate, accessible, affordable, scalable and sustainable person-centric digital health solutions to prevent, detect and respond to epidemics and pandemics, developing infrastructure and applications. This should enable countries to use health data to promote health and wellbeing, and to achieve the health-related Sustainable Development Goals[3] and the triple billion targets of WHO's Thirteenth General Programme of Work, 2019–2023[4].

The digital transformation of healthcare and therapeutic development, including exploring Artificial Intelligence (AI) uses, has proven potential to enhance health outcomes by improving medical diagnosis, digital therapeutics, clinical trials, self-management of care, and person-centered care, as well as creating more evidence-based knowledge, skills, and competence for professionals to support health care. The possibility and potential of AI-guided machines solving problems that previously were thought to require human intelligence has therefore, generated significant interest in the uses of such technologies. With the increasing availability of healthcare data and the rapid progress of analytics techniques, AI has the potential to transform the health sector, one of the most important sectors for societies and economies worldwide.

# 2. Purpose

In order to facilitate the safe and appropriate development and use of AI solutions[5] in healthcare, the International Telecommunication Union (ITU) and the WHO have established a Focus Group on AI for Health (FG-AI4H). To support its work, FG-AI4H created several working groups, including a Working Group on Regulatory Considerations (WG-RC) on AI for Health. The WG-RC consists of multiple stakeholders including representatives from regulatory bodies, policy makers, academia, and industry who explored regulatory and health technology assessment considerations and emerging "good practices" for the development and use of AI in healthcare and therapeutic development.

This publication is a general, high-level, and nonexclusive overview of key regulatory considerations' topic areas developed by the WG-RC to support the overarching FG-AI4H framework. Recognizing that a single publication cannot address the specifics of the various AI solutions that can be used for therapeutic development or healthcare applications generally, the WG-RC's overview will highlight some of the key regulatory principles and concepts, such as risk/benefit assessments and considerations for the evaluation and monitoring of the performance of AI solutions. Throughout the process of developing this publication, the WG-RC took into consideration different stakeholder perspectives, as well as different global and regional settings. The WG-RC's overview is not intended as guidance, as a regulatory framework, or policy. Rather, it is meant as a listing of key regulatory concepts and a resource that can be considered by all relevant stakeholders in medical device ecosystems, including but not limited to, developers who are exploring and developing AI solutions, regulators who might be in the process of identifying approaches to manage and facilitate AI

[2] Global Strategy on Digital Health 2020– 2025. Geneva: World Health Organization; (2020) (https://www.who.int/docs/default-source/documents/gs4dhdaa2a9f352b0445bafbc79ca799dce4d.pdf?sfvrsn=f112ede5_58)
[3] The 17 Goals - Sustainable Development. United Nations; (2020) (https://sdgs.un.org/goals)
[4] Thirteenth General Programme of Work 2019−2023. Geneva: World Health Organization; (2020) (https://www.who.int/about/what-we-do/thirteenth-general-programme-of-work-2019---2023)
[5] For the purposes of this document, "AI solutions" includes multiple technologies such as machine learning, deep learning, computer vision, neural networks, Natural Language Processing (NLP), and data mining that, individually or in combination, add intelligence to applications.



**Commented [PB2]:** Do we want to use this as definition of AI in this document? Machine-based solutions/tools able to solve problems that require human intelligence. I am in favour of adding a definition as asked below by another contributor, but I think it should be quite general in order to future-proof this document. The AI field changes so quickly that a list will be old as soon as we write it.

**Commented [MR3R2]:** I would ageee that a standard definition would be useful, perhaps to be enumerated in the definitions section below. There is a defintiion included in the ethics guidance, but it may also be worth considering any recent definition used by a regulatory agency.

**Commented [dr4R2]:** Yes agree need to have ML/AI definition early in the document

**Commented [OMP5R2]:** Agree, but let's state something like, "for the purpose of this document, the term artificial intelligence is defined as……."

I think we should state that whenever there are multiple reasonable definitions.

**Commented [SA6R2]:** This is not a definition, but this thread of comments in relation to definitions and terms to be used for the purpose of this document is very valuable and we took a long time finding the best way to address it. Below outlines the decision made and the rationale behind it:

1- It is difficult to be comprehensive as well as inclusive when it comes to AI-relevant terms and definitions beyond the scope of this WG-RC. Tis would result in lengthy publications that is not concise.
2- General AI-related terms are still very important to set the scene for general stakeholders who are targeted by this publication, and thus, we identified the need for a document that sets all common AI terms across the FGAI4H.
3- We proposed this need at the FGAI4H management meeting and this has been embraced and we are contributing to a drafted document of common terms that is aimed for delivery by September. It will be reviewed by all WG and co-chairs for consistencies.
4- For the purpose of this draft v3.x, we have moved all of the terms and definitions into an Annex and will filter this list later with terms that falls within this WG-RC for a focused publication. Those terms along with the remaining general terms will be found in the general terms document, and will be referred to in this document.

solutions, manufacturers who design and develop AI-embedded medical devices, and health practitioners who deploy and use such medical devices and AI solutions.

## 3. Acronyms, Definitions, and Fundamental Concepts

For the purpose of this document, some key terms and definitions are defined in Annex A.

## 4. Key AI Applications in Healthcare

Rapid prototype technologies have been developed with increasingly robust health and engagement claims. The blending of technology and medicine in research and development is facilitating a wealth of innovation that continues to improve[6]. Many health-related AI solutions already exist or are continuously being developed to meet a variety of stakeholders' needs in healthcare and therapeutic development. These solutions have wide-ranging uses across the spectrum of healthcare delivery and therapeutic development. For example, AI solutions in healthcare are being used to support patients throughout the phases of a disease, such as solutions to support adherence to therapeutics and enhance communication capabilities with care providers.

Healthcare is striving to become more patient-centric by using a personalized, evidence-based approach to decision-making[7]. This allows data to be used to improve patient and population wellness, patient education and engagement, prevention and prediction of diseases and care risks, medication adherence, disease management, disease reversal/remission, and individualization and personalization of treatment and care. AI solutions are being used in drug development, including drug discovery to identify potential therapeutic candidates and for modelling and prediction and in clinical research for patient enrichment. AI is also being increasingly incorporated and utilized in medical devices; diagnostic tests; clinical decision making, such as AI solutions that facilitate clinical studies and clinical evaluations; support diagnostics and disease staging efforts; care triaging; and to determine appropriate therapeutics and course of therapy. Therefore, most AI applications can be categorized in a generic framework and they may fall into one or more of the following categories[8,9]: prevention, diagnosis, screening, prediction, surveillance, drug development, end of life care, behavior modification, treatment, follow-up care, personalized treatment, care triaging, and resource allocation and health management. Figure 1 below illustrates generic non-inclusive areas of AI research and development across the spectrum of healthcare delivery and therapeutic development.

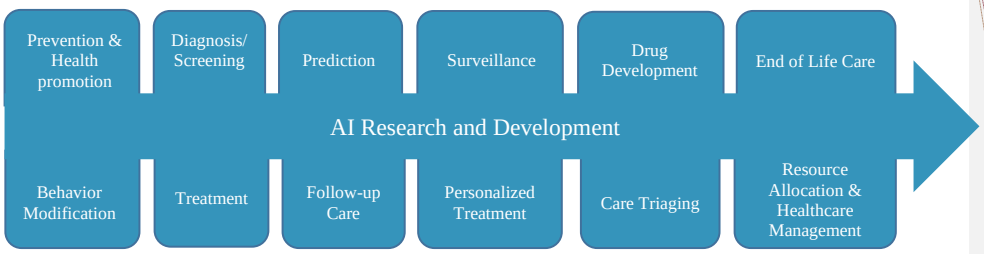


*Figure 1 A general spectrum of AI research and development in healthcare delivery and therapeutic development.*

[6] Arjun Panesar. *Machine Learning and AI for Healthcare*. Berkeley, CA: Apress. (2019) (https://doi.org/https://doi.org/10.1007/978-1-4842-3799-1).

[8] Ibid

[9] Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. Science. 2019 Oct 25;366(6464):447-453. doi: 10.1126/science.aax2342. PMID: 31649194. https://science.sciencemag.org/content/366/6464/447



**Commented [M(7]:** "in the" or "in a" ?

**Commented [SA8R7]:** Thank you for your suggestion, but we will keep it.

**Commented [aa9]:** I believe there are other aspects of health are missing in the framework . To which extend this is should be inclusive ?

**Commented [OMP10R9]:** It will be difficult to be fully inclusive and we can acknowledge that this document is not aiming to be fully inclusive. This is appropriate as there are many evolving uses.

**Commented [SA11R9]:** Thank you for your comments and I agree with the fact that this list is not inclusive. Therefore, I have updated the text to reflect on the fact that this list is not inclusive.

**Commented ['W12]:** Please consider adding a few boxes with concrete examples of AI solutions in health care.

**Commented [SA13R12]:** Figure updated.

**Commented [PB14]:** These two sentences refer to drug development. they might be combined: "AI solutions such as modelling and prediction tools can be used to support development of both medical devices and drugs. AI can also the development of diagnostic tests, therapeutic determination...

**Commented [PB15R14]:** AI can also support the development of diagnostic tests, disease stagint efforts and clinical decisions making regarding appropriate diagnostic pathway and/or course of therapy.

**Commented [OMP16R14]:** See edits. Drug discovery goes beyond compound identification. Also, I made the language clear to avoid any confusion.

I removed combination therapy as that may include a variety of combinations that may or may not be relevant to AI

**Commented [SA17R14]:** Changes to the text have been made. Please check.

**Commented [PB18]:** personalised or personalized? please decide if we will use British or American English spelling.

**Commented [SA19R18]:** Thank you for the comment and we should stick to the American spelling throughout.

The above non-inclusive spectrum helps determine what regulatory considerations are applicable and how to implement such considerations. This is mainly due to the fact that regulatory considerations may vary depending on a number of factors. This publication articulates in the remaining sections these specific regulatory considerations, as well as their factors, and discusses the topic areas relevant to all stakeholders in the current AI for health ecosystem.

## 5. Topic Areas of Regulatory Considerations

As mentioned previously, AI solutions may be utilized across all aspects of healthcare and therapeutic development. Regardless of the AI solution application category, regulators are keen not only to ensure that the AI solutions are safe and effective for intended use, but also that such promising tools reach those who need them as fast as possible. Dialogue between all stakeholders participating in the AI for health ecosystem, especially developers and regulators, is highly advised as the community matures. Therefore, this publication aims to establish a common understanding around the use of the AI solutions in health that can be relevant to all of those stakeholders.

Towards achieving this aim, an extensive literature review, which included current guidelines, allowed the identification of a list of topic areas of regulatory considerations for the use of AI in healthcare and therapeutic development. At its first meeting, the WG-RC discussed the proposed topic areas and agreed to focus its deliverable on the six key areas listed in Table 1 and discussed in the remaining sections of this publication. The working group was divided into six subgroups composed of subject matter experts to draft a section on each topic area.

*Table 1 Six Key Topic Areas of Regulatory Considerations.*

| Topic Area No. | Topic Area |
|---|---|
| Topic Area # 1 | Documentation & Transparency |
| Topic Area # 2 | Total Product Lifecycle Approach & Risk Management |
| Topic Area # 3 | Data Quality |
| Topic Area # 4 | Intended Use and Analytical & Clinical Validation |
| Topic Area # 5 | Privacy and Data Protection |
| Topic Area # 6 | Engagement & Collaboration |

The WG-RC would like to highlight that this list is not a fully inclusive list of key considerations and hopes that this list will serve as a starting point for future deliberations and subsequent updates.

- **Documentation & Transparency**

Documentation and transparency are critical concepts that are essential not only to facilitate scientific and regulatory assessments of AI solutions, but also to help ensure trust by all involved stakeholders, including end-users. Documentation and transparency help establish confidence and trust not only in the AI solution itself, but also between the developers and end-users. Accurate and comprehensive documentation is key to allowing a transparent evaluation of AI solutions for health. This includes undertaking a total lifecycle product approach to prespecifying and documenting processes, methods, resources, and decisions made in the initial conception, development process, validation, deployment, and post-deployment of health-related AI solutions that may require regulatory overview. The concepts of documentation and transparency are not new and are utilized by multiple stakeholders for different purposes. Transparency is multifaceted and developers should take into consideration the

**Commented ['W20]:** Is it "documentation" or "documenting"? In the latter case, this refers to the process of logging business processes and (automated) decisions.

**Commented [PB21R20]:** I would keep documentation because it refers to all the information/documents that needs to be shared to make sure regulatory decisions can take place

**Commented [SA22R20]:** Agree

responsibility towards end users. The following discussion focuses on some elements relevant to documentation and transparency but is not fully inclusive of all of the factors that are relevant to this important area.

Effective documentation and transparency are key elements that support and inform regulatory decision making. They also help establish trust and confidence and guard against biases and data dredging. The same regulatory expectations and standards that ensure the safety and effectiveness of regulated therapeutics still apply for when AI solutions are used in regulated areas. It is important for regulators to be able to trace back the development process and to have evidence and documentation of essential steps and decision points. For example, specifying the problem that developers are attempting to address, the context in which the AI solution is proposed to function, and the selection, cleaning, and processing of data/datasets used in the development process are all essential aspects and should be carefully documented. Documentation should allow for the tracking, recording, and retaining of records of essential steps and decisions, including justifications and reasoning for deviating from prespecified plans. For example, careful consideration should be given to documenting how data used to train the model is different than sets used for external validation, or sets used after deployment. Effective documentation may also help show that the developers are taking into consideration the full complexity of context within which the AI solution is expected to operate. This will also provide details on how the AI solution is addressing the needs of end-users and may detail the reasoning to justify widening end-user base if appropriate. In absence of transparent documentation, it becomes hard to understand whether the proposed approaches will generalize from the retrospective data presented in the submission material to real-world deployments in new settings, which may markedly reduce performance[10].

Figure 3 below shows some examples of essential steps and decision points that developers are encouraged to consider for documentation purposes.

People with different skills and expertise can be involved in the ~~Different entities, disciplines, and multidisciplinary expertise are likely to be involved in the~~ development of AI solutions for health and therapeutic development. All of them need to know how to document the scientific rationale supporting relevant development and decision steps. ~~There is a need to develop a shared understanding of procedures and steps that ensure adequate documentation that supports transparency and to show that decisions were based on appropriate scientific bases.~~ It is also important to note that systems and processes used to track and document the development processes and key decision points should have an audit trial and be ~~designed to~~ protected against data manipulation and adversarial attacks~~, and to track and record access~~.

Documentation and transparency should not be viewed as a burden, but as an opportunity to show the strength of a science-based development that considers the complexity and full context in which the AI solution is expected to be utilized~~, in addition to the characteristics of end-users among other factors~~. Tools and processes for documentation should be proportional to the risks involved. Conversation with regulatory organizations prior to or at early stages of development is ~~possible and~~ encouraged and may provide vital help in informing documentation needs.

Beyond the regulatory perspective, it is important to note that effective documentation and other steps that help ensure transparency are important ways to establish trust and a shared understanding of AI solutions in general. Other steps to facilitate transparency include, but not limited to, publishing in peer-reviewed journals; sharing data and datasets; and making code available to help establish trust, foster mutual learning, and facilitate additional studies and replications. These types of approaches will help to enrich the knowledge of the community at large. Collaborations, such as Consolidated

[10] Wu, E., Wu, K., Daneshjou, R. *et al.* How medical AI devices are evaluated: limitations and recommendations from an analysis of FDA approvals. *Nat Med* **27,** 582–584 (2021). https://doi.org/10.1038/s41591-021-01312-x



**Commented [PB23]:** medicinal products and medical devices

**Commented [OMP24R23]:** Isn't this language (regulated therapeutics) inclusive of both (and biologics, combination, etc.? Recommend keeping original.

**Commented [MR25]:** Perhaps these sentences could be combined into the paragraph above?

**Commented [PB26]:** from

**Commented [lf27]:** Add reference to last weeks' Nat. Medicine paper:

https://www.nature.com/articles/s41591-021-01312-x

(see summary tweetorial if can't pass paywall): https://twitter.com/calimagna/status/1379139064717144065?s=20

**Commented [OMP28]:** This may be misunderstood as giving permission "can". I would keep the original language as it addresses the simple reality that diverse stakeholders are developing these techs

**Commented [OMP29]:** MAJOR: I disagree with these edits and I would keep the original. This is about shared understanding on how to best document and we should not add a requirement that everybody needs to know how to document. In each group, they may designate a specific individual or group to ensure that data are retained and preserved.

**Commented [OMP30]:** MAJOR: I disagree with this. Although I agree about the audit trail, this paragraph is about the systems themselves being designed to track and avoid data manipulation. Later we discussed audit trails.

**Commented [ka31]:** evidenced-based?

**Commented [ka32]:** Do we need to limit this to peer-reviewed academic journals? A lot of developers publish findings and learnings on GitHub (falls under your code statement) or blogs or informal forums. While these are necessarily peer reviewed they are a form of communication to foster open source development that tech communities use

**Commented [OMP33R32]:** This is not limited, the rest of the sentence show ways beyond publication. I would keep the original.

Standards of Reporting Trials for AI (CONSORT-AI) [11], and Standard Protocol Items: Recommendations for Interventional Trials for AI (SPIRIT-AI) [12] have provided reporting considerations for randomized controlled trials and trial protocols when AI solutions are used. Transparency is not only an important consideration for building trust, but it also can be an essential tool to communicate and educate end-users. This can be done by customizing communications and publications to serve the needs of end-users and other stakeholders if appropriate. Also, academic institutions, medical journals, and regulatory organizations among other stakeholders are working on advancing transparency for the use of AI in therapeutic development.

**Commented [ka34]:** How? Be good to provide information on what exactly these institutions are doing to advance transparency i.e., the update to CONSORT and SPIRIT for AI mentioned above is one.

As outlined in Figure 3 below, the development process of an AI solution is multifaceted. A planned and methodical approach to documentation throughout the full development cycle, including deployment and post-deployment should be considered.

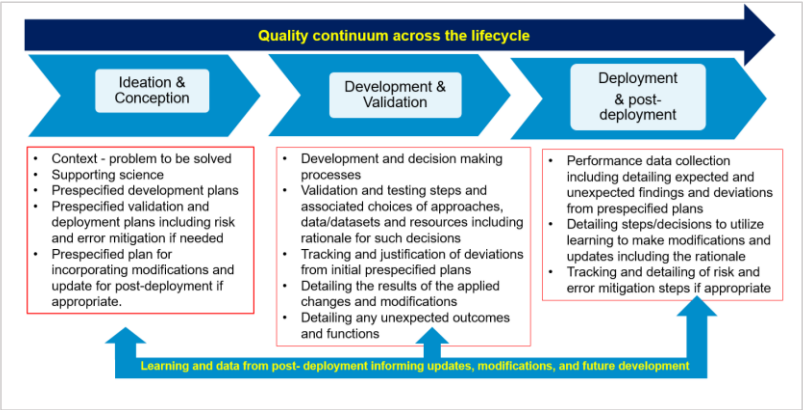


*Figure 2 Examples of key development decision points in AI solutions development* [13]

The following are some elements that might be useful to consider from a documentation and record retention perspective.

- ***Documentation across the total product lifecycle – ensuring a quality continuum***

Developers should design, implement, and document approaches and methods to ensure a quality continuum across the development phases. Effective documentation outlining all phases of development would further enhance confidence in the AI solution and would show how expected and unexpected challenges and deviations are identified and managed. Validation processes and benchmarking should be carefully documented including the decisions for selecting specific data sets, parameters, and metrics to justify such processes. For example, careful consideration should be given to documenting how and why specific data or data sets are selected to train, externally validate, and retrain the model (e.g., post-deployment retraining).

- ***Pre-specification and documenting the purpose, clinical context, and development***

[11] Liu, X., Cruz Rivera, S., Moher, D. *et al.* Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. *Nat Med* **26,** 1364–1374 (2020) (https://doi.org/10.1038/s41591-020-1034-x)

[12] Rivera Samantha Cruz, Liu Xiaoxuan, Chan An-Wen, Denniston Alastair K, Calvert Melanie J. Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI Extension *BMJ* 2020; 370 :m3210 (https://www.bmj.com/content/bmj/370/bmj.m3210.full.pdf)

[13] Modified from a presentation by M. Khair ElZarrad, U.S. FDA at the Johns Hopkins University's 2020 National Health Symposium. September 2020.

The intended purpose/function of the AI solutions should be clearly documented. The AI could be a diagnostic tool, a solution aimed at managing hospital occupancy, at augmenting or replacing clinical decision making. ~~For example, what is the problem that the AI solution is aiming to resolve~~ . Once the purpose of the AI is identified it needs to be discussed in the context of the local clinical care system taking into consideration both the standard of care and the needs of the local end-users. ~~This should take into consideration the full clinical and health contexts in which the tools are expected to function. For example, clinical care environments can be vastly complex and involve a number of individuals with different roles and expectations.~~ Documenting how the AI solution should function in such active environments needs to be considered. ~~Protocols, processes and procedures, validation steps, and any clinical studies should be prespecified and documented. Pre-specification is one of the most important elements that supports trust and confidence in the development process.~~ As shown in Figure ~~3~~A there are multiple processes, ~~plans~~validation steps and protocols that should be pre-specified and documented ~~to pre-specify the development process~~. Pre-specification is one of the most important elements that supports trust and confidence in the development process. This will show evidence ~~and~~of a coherent ~~and connected~~ development process and will be the basis for providing justifications and rationale for any future deviations and modifications.

- ***Deployment and Post-deployment***

AI solutions may be designed using data and datasets from specific populations ~~and~~, for specific end-users, and for specific contexts. If they need to be ~~As with any therapeutic, once deployed, the AI solutions will be~~ utilized in regulated areas by ~~a~~ populations and/or end-users different from those used during the training and validation phases a strong rationale should be provided and reviewed by the regulatory authorities before post-deployment changes can be implemented. ~~larger population and potentially with variable end-users. Careful planning and documentation of deployment plans and providing justification for targeting different end-users should be considered.~~ Deviations from prespecified plans and updating and/or modifying the AI solution should also be documented. Planning for post-deployment performance, data capture, and approaches to continued assessment of the AI tool should also be documented. Such approaches will be increasingly relevant once learning AI solutions that may change after deployment become more common.

- ***Risk based approach and proportionality***

Generally, regulatory frameworks highlight a risk-based approach where measures, processes, and approaches to identify and mitigate errors, biases, and other risks should be put in place in ways that are proportional to their importance. A risk-based ~~proportional~~ approach should also be considered for the level of documentation and record keeping ~~and retention~~ utilized for AI solutions. Developers of AI solutions should keep in mind that regulatory organizations have avenues for dialogue ~~and discussions~~ that can be utilized to shed light on regulatory requirements in general.

- **Total Product Lifecycle Approach & Risk Management**

Most devices that rely on AI/ML fall into the category that is commonly known as Software as a Medical Device (SaMD), which are defined by the IMDRF as "*software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device*."[14] The US Food and Drug Administration (FDA) foresees the great potential of such AI-based

**Commented [MR35]:** This seems redundant with the descriptions of AI uses above.

**Commented [OMP36]:** I would retain the original simpler language. Context can go beyond the added language and we do not want to speculate about all options. Retain original.

**Commented [OMP37]:** I agree with the rest of the edits here.

**Commented [OMP38]:** There are more global set with no specific populations identified. I would keep the "may be."

**Commented [OMP39]:** I disagree with these edits – language very confusing – take for example "utilized in regulated areas by population" that is problematic and doesn't reflect an accurate concept. Please retain original.

**Commented [aa40]:** the text of the section is not fully clear to me

**Commented [M(41]:** Terminology also adopted in other contexts.

**Commented [li42]:** The scope on whether this document covers AI medical devices or nong-medical devices is unclear. Section 6.2 (Total Product Lifecycle approach & RM) talks about AI medical devices, making reference to the definition SaMD. Section 6.1 (Documentation and Transparency) covers AI solution with an example "a solution aimed at managing hospital occupancy".

**Commented [aa43]:** There are other methodologies and some of the use cases are not covered by SaMD

[14] Software as a Medical Device (SaMD): Key Definitions. IMDRF (2013) (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf).

software as a medical device in transforming healthcare due to the potential ability to learn from real-world feedback (training) and improve performance (adaptation)[15,16].

The regulatory principles for AI-based software as a medical device are similar to typical software that are regulated as medical devices, in addition to specific considerations including but not limited to, continuous learning capabilities, level of human intervention, training of models, and retraining[17]. Furthermore, a holistic risk management approach that addresses risks associated with an AI medical device cybersecurity threats and vulnerabilities should be considered throughout all phases in the life of a medical device including pre-and post-market. This topic area aims to present a holistic risk-based approach for AI medical devices throughout its lifecycle during pre- and post-market deployment.

- ***AI medical devices during the development and deployment process***

The block diagram in Figure 1 below illustrates the process of the development and deployment of an AI medical device. Developers and implementers of AI medical devices should establish measures to ensure the responsible development of AI medical devices.

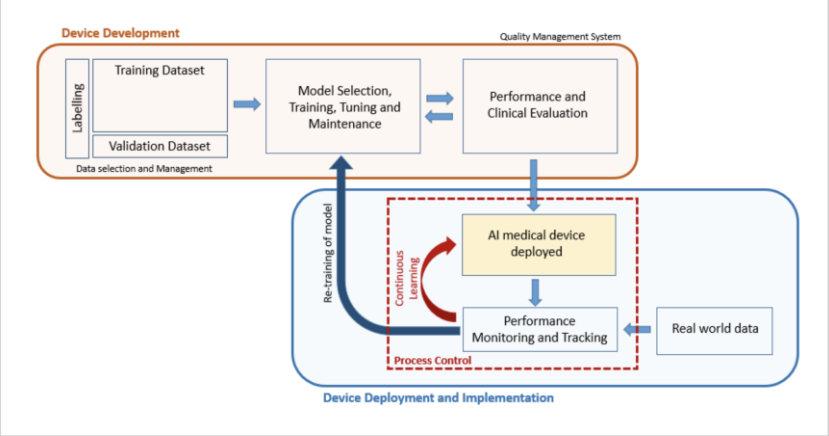


*Figure 3 The process of developing and deployment of the AI medical device[18]*

As illustrated in Figure 4 above, all activities related to the design, development, training, validation, retraining, and deployment of AI medical devices should be performed and managed under an ISO

[15] Regulatory Guidelines for Software Medical Devices – A Life Cycle Approach. Singapore; The Health Sciences Authority (2020) (https://www.hsa.gov.sg/docs/default-source/hprg-mdb/gudiance-documents-for-medical-devices/regulatory-guidelines-for-software-medical-devices---a-life-cycle-approach.pdf)

[16] Good practices for health applications of machine learning: Considerations for manufacturers and regulators Johner, Christian, Balachandran, Pradeep, Oala, Luis, Lee, Aaron .Y., Leite, Alixandro Werneck, Murchison, Andrew, Lin, Anle, Molnar, Christoph, Rumball-Smith, Juliet, Baird, Pat, Goldschmidt, Peter. G., Quartarolo, Pierre, Xu, Shan, Piechottka, Sven, and Hornberger, Zack
*In Proceedings of the ITU/WHO Focus Group on Artificial Intelligence for Health (FG-AI4H) - Meeting K* 2021

[17] Ibid

[18] Ibid

13485 based quality management system[19]. Next to clinical endpoints, AI-specific monitoring dimensions include confidence[20], bias and robustness[21], among others.

- ***AI medical device product lifecycle***

An AI medical device lifecycle approach can facilitate continuous AI learning and product improvement while providing effective safeguards. This can be achieved if such an approach involves appropriate developing practices for AI medical device and technologies throughout the development and deployment of adaptive AI medical devices. Furthermore, this approach could potentially increase the trustworthiness and safety of the solution. The FDA, based on numerous sources, including IMDRF recommendations, has proposed a Total Product Lifecycle (TLPC) approach as part of their proposed regulatory framework for modifications to AI medical device. The TLPC approach is illustrated in Figure 5 below, and it comprises the following four key components that qualify as good machine learning practices:

1. demonstration of a culture of quality and organizational excellence of the company producing the device;
2. premarket assurance of safety and effectiveness;
3. review of AI medical device pre-specifications and algorithm change protocol; and
4. real-world performance monitoring.

[19] Ibid

[20] Detecting Failure Modes in Image Reconstructions with Interval Neural Network Uncertainty
Oala, Luis, Heiß, Cosmas, Macdonald, Jan, März, Maximilian, Samek, Wojciech, and Kutyniok, Gitta
*In ICML 2020 Workshop on Uncertainty & Robustness in Deep Learning* 2020

[21] Data and artificial intelligence assessment methods (DAISAM) reference
Oala, Luis, Balachandran, Pradeep, Cabitza, Federico, Calderon Ramirez, Saul, Chiavegatto Filho, Alexandre, Eitel, Fabian, Extermann, Jérôme, Fehr, Jana, Ghozzi, Stephane, Gilli, Luca, Jaramillo-Gutierrez, Giovanna, Kester, Quist-Aphetsi, Kurapati, Shalini, Konigorski, Stefan, Krois, Joachim, Lippert, Christoph, Martin, Jörg, Merola, Alberto, Murchison, Andrew, Niehaus, Sebastian, Ritter, Kerstin, Samek, Wojciech, Sanguinetti, Bruno, Schwerk, Anne, and Srinivasan, Vignesh
*In Proceedings of the ITU/WHO Focus Group on Artificial Intelligence for Health (FG-AI4H) - Meeting I* 2020

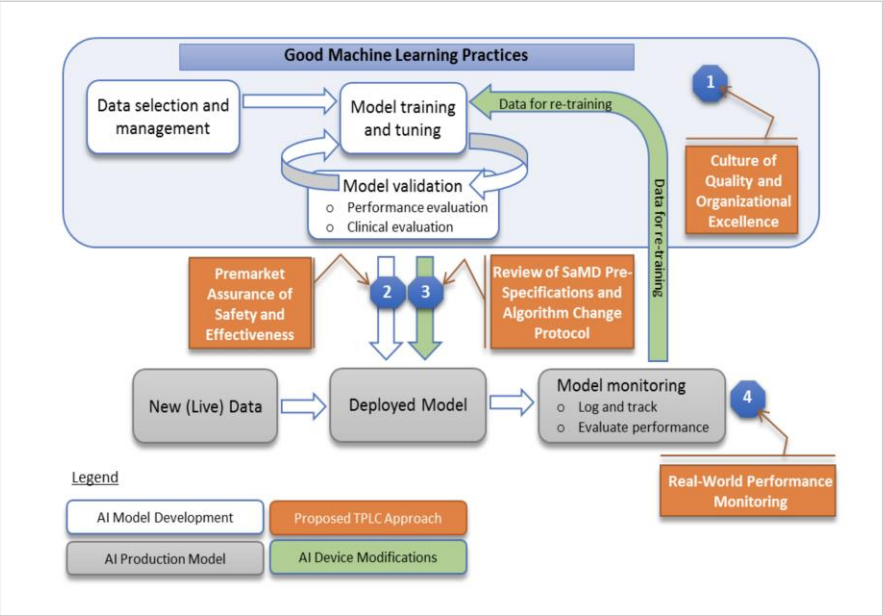


*Figure 4 AI medical Total Product Lifecycle approach on AI workflow*[22][23].

- ***Holistic risk management***

Holistic risk evaluation and management should be considered, and it should take into consideration the full context within which the AI system may be utilized. This could include not only the software or AI system being developed, but also other software that may be used within the same environment or context. Other risks, such as those associated with cybersecurity threats and vulnerability should also be considered and managed. Risks associated with cybersecurity threats and vulnerabilities should be considered throughout all phases in the life of a medical device. Therefore, AI medical device manufacturers should employ a risk-based approach to ensure the design and development of medical devices with appropriate cybersecurity protections. Doing so necessitates that manufacturers take a holistic approach to device cybersecurity by assessing risks and mitigations throughout the product's life cycle. In order to achieve this, the IMDRF has published a security risk management process, illustrated below in Figure 6.

**Commented [lf44]:** Consider adding the response to public comments of Jan 2021:

https://www.fda.gov/media/145022/download

**Commented [SA45R44]:** Thank you. Reference added.

**Commented [pa46]:** The first paragraph in this section is about cybersecurity - I expected it to be a general discussion about risk management and then there would later be discussions about specific types of risk (e.g. Cybersecurity.) Suggest either adding an introductory paragraph before doing a deep-dive into cyber, or rename this section as "Cybersecurity risk management"

**Commented [OMP47R46]:** Agreed – just to avoid additional review rounds I added language

**Commented [SA48R46]:** I also agree with Pat, thank you making such edits, it reads well.

[22] Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback. U.S. FDA Artificial Intelligence and Machine Learning. (2019) (https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-and-Machine-Learning-Discussion-Paper.pdf)

[23] FDA response to public comments on AI medical Total Product Lifecycle approach on AI workflow of Jan 2021: https://www.fda.gov/media/145022/download

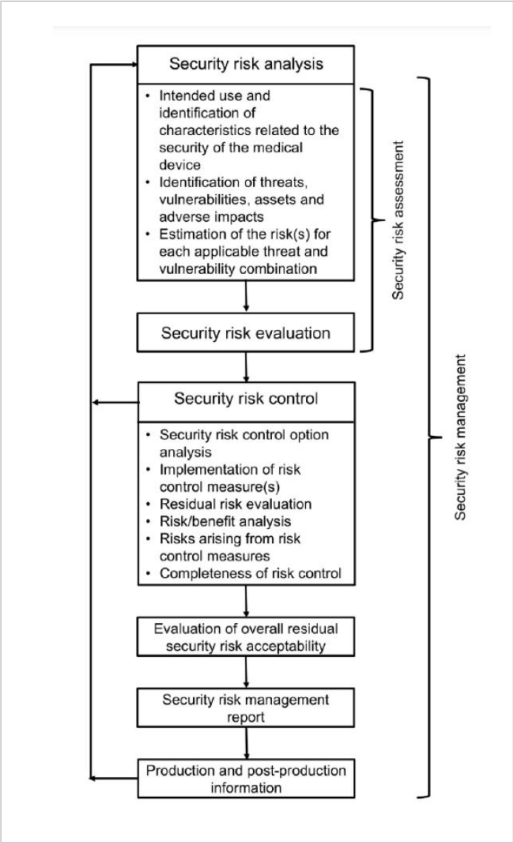


*Figure 5 IMDRF schematic representation of the security risk management process[24].*

However, to facilitate AI medical device risk management, a general holistic management approach is introduced in this subsection with three broad management categories: pre-market development management, post-market management, and change management. These categories are illustrated in Figure 4 and discussed below:


*Figure 6 General AI medical device risk management approach.*

[24] Principles and Practices for Medical Device Cybersecurity. International Medical Device Regulators Forum (IMDRF). (2019) (http://www.imdrf.org/docs/imdrf/final/consultations/imdrf-cons-ppmdc.pdf)

~~Holistic risk management must take into consideration not only the software developed, but other third party software. The risk of including third party software components in healthcare technologies can be managed, in part, by leveraging a software bill of materials (SBOM).~~

**Commented [OMP49]:** 3rd party software that interacts with the software developed…this is not clear. I think we don't need this added language as the full context should be considered. See added language to the intro.

**Commented [lf50]:** https://www.nature.com/articles/s41746-021-00403-w

- **Pre-market development management**

AI medical devices can be based on "locked" or "adaptive" algorithms. When an algorithm is locked, the algorithm provides the same result each time the same input data is applied to it and it does not change or "learn" from new data[25]. In contrast, an adaptive algorithm continuously learns from real-world experience or additional data, and the output for the same input data may be different before and after this learning occurs.

The controls and measures put in place to ensure that an AI solution functions as expected while minimizing any risk should be proportional to the risks that could be imposed if the AI solution were to malfunction. For example, failure of an AI solution that is designed to encourage adherence to a healthy diet is different than one that is designed to diagnose or treat certain diseases and pathologies. Therefore, developers should consider a risk-based approach throughout all involved processes to prioritize safety. Developers need to consider the intended use of the AI solution and the clinical context, if appropriate, to evaluate the level of risk. For example, the IMDRF risk framework for SaMD identifies two major factors that may also contribute to the impact or risk of AI medical devices. The first factor is the significance of the information provided by the AI medical device to the healthcare decision. The significance is determined by the intended use of the information – to treat or diagnose, to drive clinical management, or to inform clinical management. The second factor is the state of the healthcare situation or condition, which is determined by the intended user, disease or condition, and the intended population for the AI medical devices – critical, serious, or non-serious healthcare situations or conditions. Taken together, these factors describing the intended use can be used to place the AI medical device- into one of four categories from lowest (I) to highest risk (IV) to reflect the risk associated with the clinical situation and device use.

**Commented [li51]:** The IMDRF's Framework for Risk Categorization is intended to categorize SaMD. The software must first be a medical device. The framework is not intended to categorize risk of AI-solution that is non-medical device. The example given here is "AI solution that is designed to encourage adherence to a healthy diet" (highlighted) is out of the scope of IMDRF SaMD risk categorization.

**Commented [OMP52R51]:** Great catch – see minor edits to show the delineation while qualifying that IMDRF work is SaMD specific.

*Table 2 AI medical devices risk classification*[26]

| State of healthcare situation or condition | Significance of information provided by AI medical devices to healthcare decision | | |
|---|---|---|---|
| | Treat or diagnose | Drive clinical management | Inform clinical management |
| Critical | IV | III | II |
| Serious | III | II | I |
| Non-serious | II | I | I |

[25] Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback. U.S. FDA Artificial Intelligence and Machine Learning. (2019) (https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-and-Machine-Learning-Discussion-Paper.pdf)

[26] "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations. IMDRF (2014) (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf)

The intended use and risk classification should be considered when testing different models and balancing trade-offs, such as transparency and accuracy. In cases where training data sets are limited, simpler models, such as regression or decision tree models, often provide equivalent or better results than more complex models with the added benefit of more transparency and interpretability. On the other hand, in cases with larger, complex data sets, complex models, such as deep learning networks, may not lend themselves to being explainable but may provide greater accuracy than simpler models. However, in cases in which there is a greater risk of harm, stakeholders should consider discussing the risks and benefits of choosing a more complex model and whether there are ways to mitigate the lack of interpretability and transparency and build trust in the model through additional validation measures.

Furthermore, depending on the level of risk, some AI products may be approved as being available for full deployment whereas others may be initially authorized for deployment in more 'AI-ready' institutions which are certified based on having stringent levels of surveillance in place with responsive back-up systems to handle any failure of the algorithm to minimize risk of patient harm.

Overall, it is important to achieve transparency and trust between all AI solution stakeholders including the developers/ manufacturers, regulatory authorities, and the implementors (i.e. users in the healthcare settings such as medical practitioners). Appropriate documentation of risk management and proper auditing procedures are examples of ways that help assure transparency. Ideally, it is important to audit specific components of the AI medical device (i.e. software, hardware, training data, failure cases!). For instance, it is important to version control training data, as more data is added with each update. If an algorithm suddenly deteriorated in performance after an update, we may wish to inspect everything that contributed to the update. In most cases, the thing that will have changed is the addition of new training data by the developer (rather than changes to the software itself, such as modification to the neural networks). Moreover**,** given how unpredictable changes in performance can be for AI, it is recommended to have active reporting and investigation of failure cases (in the CONSORT-AI guidelines) although it is not prescriptive due to the wide range from common-sensical clinical auditing (i.e. human inspection) to technical solutions based on inference.

Finally, there is a thickening web of country-, nation-, and jurisdictional-specific legislations and laws that manufacturers and developers may need to consider for the development and deployment of regulated AI medical devices in healthcare. Such legislation includes, but is not limited to, the Personal Data Protection Act, Human Biomedical Research Act, Private Hospitals and Medical Clinics Act, Health Insurance Portability and Accountability Act, and General Data Protection Regulation (GDPR). Therefore, compliance with relevant laws (local, and cross-jurisdictional laws and data protection acts) needs to be demonstrated by manufacturers and developers of AI medical devices.

- ***Post-market management***

Post-market monitoring and surveillance of AI medical devices allows timely identification of software and hardware related problems, which may not be observed during device development, validation, and clinical evaluation since these are performed in controlled settings. New risks may surface when the software is implemented in a broader real-world context and is used by a diverse spectrum of users with different expertise. Companies involved in distributing AI medical devices (manufacturers, importers, wholesalers and registrants) are required to comply with their post-market

**Commented [li53]:** and patients.

**Commented [OMP54R53]:** It depend on the use. Many AI systems are intended for healthcare providers or auxiliaries. I would keep as is.

**Commented [pa55]:** I don't believe that transparency can always be achieved by risk management documentation nor by auditing. Good practices can be demonstrated by disclosures and audits, but this does not assure transparency -- the neural net might still be a "black box". Suggest removing these sentences.

**Commented [OMP56R55]:** Agreed – see edits

**Commented [MR57]:** Perhaps some repetition with the discussions of transparency and documentation above, although I understand this to be specific to risk management.

**Commented [OMP58R57]:** This is an important area to stress even at the risk of being repetitive.

**Commented [pa59]:** I expected that there would be a discussion about bias & risk management. Although bias is mentioned a few times in the document, I expected there to be a discussion about how bias can lead to unacceptable risk, I expected there to be a plan on how to assess for bias in the training data, how to test for it, and even post-market monitoring for bias that was originally missed, or "drift" in healthcare that leads to emerging bias effects.

**Commented [OMP60R59]:** If Pat would like to add some language that will be welcomed

**Commented [li61]:** PDPA and GDPR should be applicable for the development and deployment of non AI-MD. This paragraph seems to suggest that development and deployment of non-AI MDs are excluded from these legislation.

**Commented [OMP62R61]:** Added "may" as applicability varies and to show that these regs are not only applicable to AI.

duties and obligations which includes reporting of device defects or malfunctions, recalls, Field Safety Corrective Actions, and serious injuries or death associated with use of the device[27].

Furthermore, manufacturers should have an initiative to actively survey and detect possible threats as part of their post-market plan. There should be a plan outlined by the manufacturers on how they can actively monitor and respond to evolving and newly identified threats. Key considerations for the post-market plan include[28]: post-market vigilance, vulnerability disclosure, patching and updates, recovery, and information sharing. Finally, as part of the post-market duties and obligations, companies involved in distributing medical devices (manufacturers, importers, wholesalers and registrants) are required to report adverse events associated with the use of software medical devices.

Generally speaking, there is a need for both continuous post-market clinical performance follow up and a periodic safety summary report. The intensity of post-marketing surveillance should also be risk-proportionate (according to consequences of failure and likelihood of early detection of failure). Finally, post-market surveillance requires a minimum level of evaluation for each site to ensure that potential algorithm vulnerabilities due to variation in local environments can be detected.

**Commented [pa63]:** Would a periodic management review (13485, 14971) be the proper place to hold the "periodic safety summary" ? This might be easier for organizations if we can show them that this is something they are mostly doing anyway, and we aren't asking for something completely new.

For example, the UK National Health Service (NHS) AI Lab published a guidance to accelerate a safe and effective adoption of AI in health. This guide lists ten questions, falling under four categories, to help buyers of AI products make informed decisions, : problem identification, product assessment, implementation considerations, and procurement and delivery (as illustrated in Figure 8 below).

**Commented [li64]:** Could this be a new section? The content is more than “post market management”.

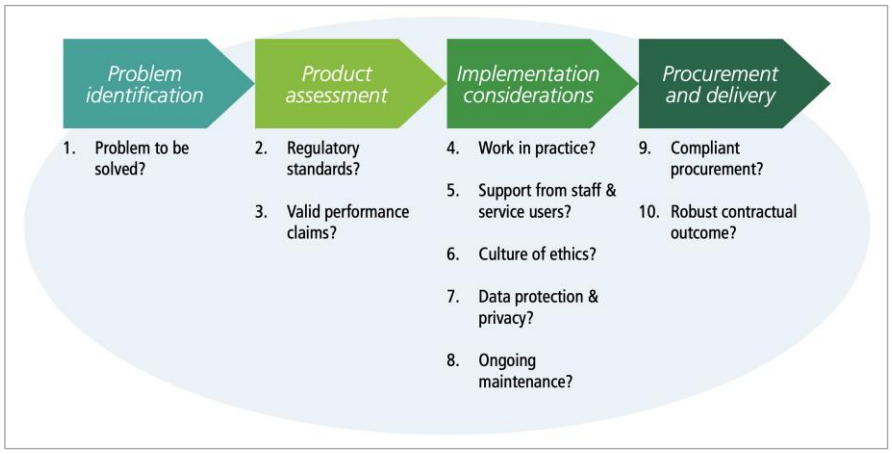


*Figure 7 The UK NHS Buyer's Guide to AI in Health and Care[29]*

- ***Change management***

Considering the character of AI medical devices, it is significant to settle the regulatory system for enabling continuous improvements through the product lifecycle. One of the models is the

[27] Regulatory Guidelines for Software Medical Devices – A Life Cycle Approach. Singapore; The Health Sciences Authority (2020) (https://www.hsa.gov.sg/docs/default-source/hprg-mdb/gudiance-documents-for-medical-devices/regulatory-guidelines-for-software-medical-devices---a-life-cycle-approach.pdf)
[28] Ibid
[29] A Buyer's Guide to AI in Health and Care. NHSX; UK (2020) (https://www.nhsx.nhs.uk/ai-lab/explore-all-resources/adopt-ai/a-buyers-guide-to-ai-in-health-and-care/)

change management approach implemented by the Ministry of Health, Labour and Welfare (MHLW) of Japan. This approach is adapted in the Pharmaceuticals and Medical Devices Act as Post-Approval Change Management Protocol (PACMP) for medical devices[30]. Basic concept was published by the International Conference of Harmonization in the field of pharmaceutical area and this concept is also available to the medical devices such as AI with continuous improvements through the product lifecycle[31]. The PACMP is illustrated below in Figure 9.

**Commented [MR65]:** Layperson question: How does this differ from the Total Product Lifecycle Approach discussed above (from the USFDA)?

**Commented [OMP66R65]:** My understanding is that there are minor differences, but not sure.

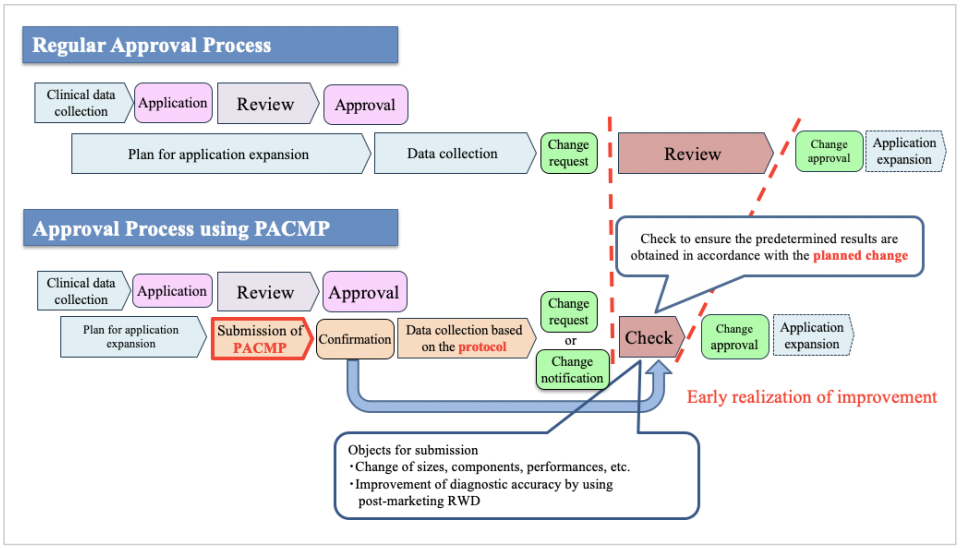


*Figure 8 Post-Approval Change Management Protocol (PACMP) for medical devices.*

- **Intended Use and Analytical & Clinical Validation**

In principle, regulatory mechanisms are in place to answer the question: Do the available data (included in regulatory submission) support the conclusion that an investigational or experimental therapeutic is safe and effective to justify entry into the market and public access? In addition to the principles in 5.1 and 5.2, assessing if the use of the solution is safe (will not harm the user) and if the claims made about the performance are robust (efficacy) should also be considered (see Figure 10 below). To evaluate these claims for AI tools requires a clear use case description, demonstration of analytical and clinical validation, and assessment of the potential for bias or discrimination in the tool.

[30] "Handling with applications for confirmation of PACMP for medical devices" MHLW PSEHBSD Notification No.0831-14, August 31, 2020. https://www.mhlw.go.jp/content/11120000/000665757.pdf

[31] International Conference of Harmonization harmonised guideline: Technical and regulatory considerations for pharmaceutical product lifecycle management Q12. https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf


*Figure 9 Domains of health technology regulation, assessment and management for drugs and devices*

- ***Use case description, analytical, and clinical validation***

Demonstrating safety and consistently delivering expected performance is a critical part of regulation. Independent evaluation of a tool is important, not only for clinicians and patients and other end users of a product, but also as a quality mark for developers and procurers. For AI tools, setting out best practice in analytical and clinical validation is challenging. Not only is the regulatory landscape changing, but the technical capabilities underpinning many tools is developing rapidly, and there is a growing body of research on digital and AI interventions in health.

The performance of AI solutions can be rapidly changed, not only as a result of code change, but also with the provision of different or additional training or tuning data. Evaluation that considers steps from development, to analytical and clinical validation, and post market surveillance is therefore considered best practice for AI tools, as described by the FDA as a Total Product Lifecycle approach to development and validation of AI-based devices[32] (see Figure 5).

This topic area covers the concepts of use case description (including intended use statements) and analytical and clinical validation. It describes the key regulatory and health technology considerations and best practices, and builds on important work from international regulatory and national bodies for example the IMDRF and FDA. It is not intended to replace this guidance. By outlining key considerations, this deliverable describes where challenges remain in this rapidly changing field. For example particular consideration is given to under-resourced settings which may have less national regulatory capacity. This document also explores the role of benchmarking in the evaluation of AI solutions in health, and relates these evaluation principles to this topic area, and to the WHO/ITU FG-AI4H work, in which benchmarking exploration is a key component[33].

- ***Intended Use***

AI solutions are complex, dependent not only on the constituent code, but also on the training data, clinical setting, and user interaction. They are often situated in a complex clinical pathway or are being introduced in new clinical pathways altogether (for example, into new telemedical pathways or part of the addition of new triage tools). Therefore, for AI tools, safety and performance can be highly context dependent. The description of use case has a substantial role both to inform end users where the tool can safely and appropriately be utilized, and for regulated tools (the statement of intended

**Commented [li67]:** The FDA's document refers to AI based SaMD. We need to clarify if these terms used in this documents ("AI solutions"/ "AI tools"/ "AI-health related tool" / "AI-based tools") refer to MD or non-MD. Need to standardized the term use.

**Commented [L(68R67]:** Shada - what did you decide we would use at the standard term here?

[32] Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback. U.S. FDA Artificial Intelligence and Machine Learning. (2019) (https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-and-Machine-Learning-Discussion-Paper.pdf)

[33] Schörverth, Elora, et.al. FG-AI4H Open Code Initiative - Evaluation and Reporting Package. *In Proceedings of the ITU/WHO Focus Group on Artificial Intelligence for Health (FG-AI4H) - Meeting K* 2021

use), to allow regulators to assess if the evidence of the analytical and clinical validation steps taken are appropriate and sufficient for the use case intended.

When developing an AI-health related tool, it is important for stakeholders to consider and describe the use case of the tool. This consideration should cover the setting (geography, type of care facility), the population (ethnicity, race, gender, age, disease type, disease severity, co-morbidities) the intended user (healthcare provider or patient facing), and the clinical situation for which it is intended. This is a particularly important consideration for AI tools, as unlike other health interventions and tests, AI-based tools are highly sensitive to the characteristics of the data they were trained upon and are prone to failure in unseen data types (such as a new disease feature or population type or context that was previously unencountered). Developers should also provide a clear clinical and scientific explanation of the tools' intended performance, including the populations and contexts in which it has been validated for use. Standardized reporting templates common to all stakeholders can help to more effectively communicate the intended use[34,35,36]. For some intended use cases there may be clear reasons why analytical performance of the tool would differ in different settings[37] (for example a symptom checker may perform differently in areas with different disease epidemiology to the data on which it was trained). If this is the case, systematic known differences in performance should be included in the intended use statement. For other intended use cases, there may be emerging evidence that the tool under consideration, or other very similar tools, have been shown to have similar analytical performance in a wider setting than those in which they were initially developed and validated[38] (for example retinal tools have been shown to have a similar performance in different populations[39]). Understanding of the generalizability of similar tools may be considered when providing a statement of the intended use or description of the use case[40].

As part of the risk management process, regulators may wish to request evidence that developers have considered if there are situations in which a tool should not be used (for example if there is insufficient training data for a particular patient group, or absence of validation in a particular setting), or if there are potential risks from use outside of intended settings.

- ***Analytical Validation (also referred to as technical validation)***

For the purposes of this document, analytical validation refers to the process of validating the AI tool using data, but without performing interventional or clinical studies. This may also be referred to as technical validation. Appropriate analytical validation demonstrates that a model is robust and performs to an acceptable level in the intended setting. It also enables the understanding of potential bias and generalizability (and any steps taken to understand these).

Developers should provide a description of training datasets used in model development, tuning, and internal validation. (as for the intended use case description, this should cover the size, setting,

[34] Sendak, M. P., Gao, M., Brajer, N., & Balu, S. (2020). Presenting machine learning model information to clinical end users with model facts labels. *NPJ digital medicine*, *3*(1), 1-4.
[35] Data and artificial intelligence assessment methods (DAISAM) Audit Reporting Template
Verks, Boris, and Oala, Luis
*In Proceedings of the ITU/WHO Focus Group on Artificial Intelligence for Health (FG-AI4H) - Meeting J* 2020
[36] *Luis Oala, et. al.* ML4H Auditing: From Paper to Practice.*Proceedings of the Machine Learning for Health NeurIPS Workshop*, PMLR 136:280-317, 2020.
[37] Post-Hoc Domain Adaptation via Guided Data Homogenization
Willis, Kurt, and Oala, Luis
*In ICLR 2021 Workshop on Robust and Reliable Machine Learning in the Real World Workshop (RobustML)* 2021
[38] More Than Meets The Eye: Semi-supervised Learning Under Non-IID Data
Calderon-Ramirez, Saul, and Oala, Luis
*In ICLR 2021 Workshop on Robust and Reliable Machine Learning in the Real World Workshop (RobustML)* 2021
[39] Artificial intelligence using deep learning to screen for referable and vision-threatening diabetic retinopathy in Africa: a clinical validation study. Bellemo et al. The Lancet Digital Health. Vol 1, Issue 1, 35-44. 2019.
[40] Macdonald J., März M., Oala L., Samek W. (2021) Interval Neural Networks as Instability Detectors for Image Reconstructions. In: Palm C., Deserno T.M., Handels H., Maier A., Maier-Hein K., Tolxdorff T. (eds) Bildverarbeitung für die Medizin 2021. Informatik aktuell. Springer Vieweg, Wiesbaden. https://doi.org/10.1007/978-3-658-33198-6_79

population demographics, intended user and clinical situation (with input and output data), and can use standardized reporting templates). Transparency and documentation around dataset selection and characteristics are critical to ensure that tools are used appropriately Developers and regulators may expect that the AI tool has been externally validated in a dataset that is independent from that in which it was trained in order to demonstrate external validity and generalizability of the model beyond the dataset in which it was trained. The external dataset is expected to be representative of the setting and population that are described in the intended use (gender, race, ethnicity) to demonstrate robust performance in the intended setting. The validation dataset should be of adequate quality, with appropriate robustness of labels. As part of risk management process, it is important to identify any high-risk cases or cases that may be[41].

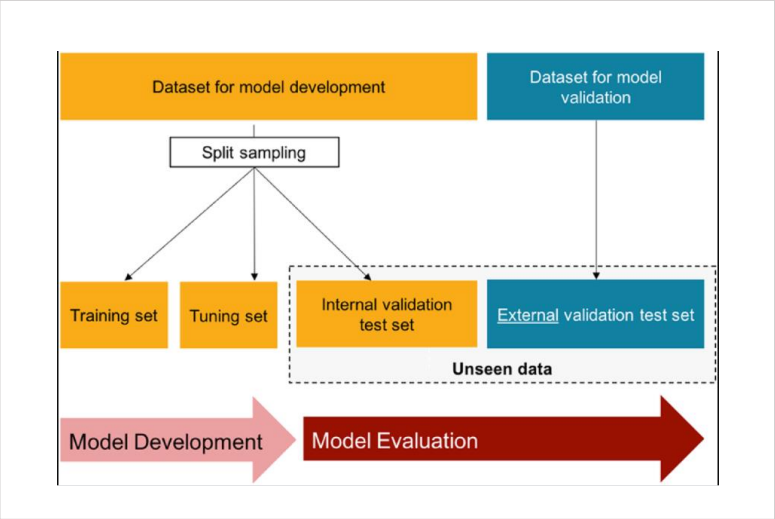


*Figure 10 Overview of datasets involved in a machine learning diagnostic algorithm: model development and evaluation*[42]

Although bias, errors, and missing data are not unique to AI development, they are still serious concerns, which may arise for many reasons including unequal and non-representative training or validation datasets or structural bias in the systems where training data is generated (e.g., healthcare settings). Reporting the gender, race and ethnicity of individuals in the training and validation data cohorts, if feasible, would help in addressing the potential for bias and its impact. For example, a better understanding of bias may help identify populations for which the tool may not function as expected. Post marketing surveillance could also provide insights into the impact of potential bias.

Obtaining datasets that are sufficiently representative, and of sufficient quality can be difficult. Those local, regional, and national bodies interested in procuring AI solutions could hold their own hidden dataset to enable this external validation set (for example, a scheme currently underway by the UK body NHSX, which has nationally representative datasets for some common use cases). Access to representative datasets for validation is a particular issue in many low- and middle-income countries. Where datasets are available in low resource settings, there may also be limitations introduced by the quality of the data. The ability to produce robust datasets with high quality ground truth labels is likely to be affected by limitations elsewhere in the health setting where there are barriers impeding access to diagnosis and treatment. These major challenges have the potential to not only propagate

[41] Oala, L. et. al. (2020, November). ML4H Auditing: From Paper to Practice. In *Machine Learning for Health* (pp. 280-317). PMLR.
[42] A Clinician's Guide to Artificial Intelligence: How to Critically Appraise Machine Learning Studies. Faes et al. TVST. Feb 2020, Vol 9,7.

inequality of access, but also to compromise safety and performance of AI tools, and is a potential area of future work (for example the newly launch iDAIR collaborative mentions use of collaborative, distributed, and responsible use of data as one of their main aims[43]).

While most regulatory agencies have national or regional remits, there is currently a reliance within some countries with limited regulatory capacity on decisions made by other major regulators. Availability of independent, hidden, representative datasets also offers particular advantages to countries that do not have their own regulatory process, or where regulatory decisions may be informed by data provided to other bodies. The performance of AI tools is highly dependent on the context. Local or national bodies could perform analytical validation as a second local validation step to ensure that the performance metrics obtained are consistent with that demonstrated for other regulatory approvals. This could be best prioritized through a needs-based approach, for example, the identification of key areas in which AI tools are promising and could provide local value, and the potential prospective creation of datasets to support validation.

In order to understand the performance of the tool, evaluation against an accepted standard should be made. The most appropriate standard for comparison may differ by intended use but commonly used standards are human performance in a similar task or other models (for example derived from logistic regression) with strong evidence-based or mandated standards of accuracy, sensitivity and specificity (for example for screening tools). Depending on the intended use case, the requirement for comparative performance may be more or less stringent (for example when used as a triage or screening tool, a different level of comparative performance may be acceptable compared to a tool used for diagnosis).

Some limited comparative benchmarking of AI solutions has been performed in a single setting but may become more common as the number of available tools increases[44]. In the future, if an AI tool has proven clinical efficacy and safety in a particular setting, it may be possible and appropriate to benchmark other newer tools against these to understand potential similarity of performance. Benchmarking software is being developed as part of the work of the Open Code Initiative[45]. Platforms like this may also be useful as a way to perform repeated algorithmic validation of models that been updated. However, this is currently not the case for any use cases, and benchmarking thus far has been used to understand comparative analytical performance.

A designated FG-AI4H working group on Data and AI Solution Assessment Methods[46] provides guidance on the methods, processes and software development for the analytical validation of health AIs[47].

- ***Clinical validation***

Analytical validation performed retrospectively on an existing dataset gives measures of performance (accuracy, negative predictive value, positive predictive value), but does not allow evaluation of other factors that may affect performance of the tool (user interaction, workflow integration and unintended consequences of tool within a complex clinical pathway).

Both national and international bodies have proposed a graded set of requirements based on risk for digital health tools (significance of the information provided by the tool and the state of the health

[43] Advancing Digital Health and Artificial Intelligence Research through Collaboration. I-DAIR. (2020) (http://i-dair.org/)
[44] Salim, M., Wåhlin, E., Dembrower, K., Azavedo, E., Foukakis, T., Liu, Y., Smith, K., Eklund, M., and Strand, F. (2020). External Evaluation of 3 Commercial Artificial Intelligence Algorithms for Independent Assessment of Screening Mammograms. JAMA Oncology
[45] https://www.itu.int/en/ITU-T/focusgroups/ai4h/Pages/opencode.aspx
[46] https://aiaudit.org/
[47] Oala, Luis et.al. ML4H Auditing: From Paper to Practice *In Proceedings of the Machine Learning for Health NeurIPS Workshop* 2020

condition)[48,49]. The IMDRF document on clinical evaluation of SaMD (illustrated earlier in Table 2[50]) proposes that tools in category I are the lowest risk tools, and that a novel tool in this category would require manufacturers to collect real world performance data and a demonstration of analytical validity. For higher risk SaMD, clinical performance evidence is expected in addition to analytical validity. The appropriate level of clinical validation (or clinical performance evidence) for a novel AI tool before deployment is not universally agreed on and is the subject of a separate working group within the FG-AI4H (Working Group on Clinical Evaluation).

Randomised clinical trial data are the gold standard evaluation of comparative clinical performance, and may be appropriate for the highest risk devices, where an AI tool has no demonstrated performance in that setting or for large national procurement bodies that seek evaluation of performance before national expenditure. A trial that is expected to guide clinical practice should have a clinically meaningful primary endpoint (morbidity, mortality), but in certain situations, event rate or time lag between the trial and the endpoint may result in a more feasible surrogate endpoint. Reporting guidelines backed by the widely accepted EQUATOR network are now available for protocols and clinical trials using AI solutions[51]. However currently there remains a small number of actively recruiting or completed randomised trials in this field[52].

Randomised clinical trials have potential limitations that may make other options preferable (trials can be slow, expensive, and may evaluate performance in specific groups under trial conditions). Where randomised evidence may not be necessary (for example evidence required may be proportional to the risk or cost of a tool), prospective validation, in a real-world deployment and implementation trial, with a relevant comparison group showing improvement in meaningful outcomes using validated tools or widely accepted and verified endpoints, and with systematic safety reporting may be appropriate. For low- and middle-income countries with under-resourced settings, clinical performance should be considered in the context of the capability of the health workers, available internet bandwidth and health informatics infrastructure, and real-time data pipelines, and developers should provide a description of the steps taken to perform clinical validation in a similar context to that which is available at the intended use setting.

**Commented [MR69]:** This sounds like performance is not an absolute measurement but that in poor countries or where there is limited capacity to provide care/diagnosis etc that it would be acceptable to have a tool that does not perform as well as it would need to in the U.S. I am not sure if that is the intention, but if so, it would seem ethically dubious.

Further consideration of the most appropriate level or type of clinical evaluation for a digital health intervention will be provided by the WG on clinical evaluation.

The following special considerations are specific to

- ***Post market safety monitoring***

**Commented [li70]:** Combine with "Post Market Management" on page 18.

**Commented [L(71R70]:** I think these post market considerations fit ok here because it is part of clinical evaluation. And I don't mind the repetition, but happy to combine if others feel strongly

Post-market monitoring in some regulatory contexts can often rely on adverse event reporting. However, many bodies agree that a period of more intense monitoring is appropriate for AI based tools in health and may be more accessible than real world experience of other devices. As part of a total product lifecycle approach to regulation in this context, further prospective clinical evaluation may be completed after deployment. Regulators may be particularly interested in monitoring adverse event rates and continuous monitoring using real-world data. For prospective monitoring of real-world data, significant investment will be required in prospectively curating and labelling validation data. A defined period of close monitoring may be appropriate for AI based tools given the novelty

[48] International Medical Device Regulators Forum. (http://www.imdrf.org/docs/imdrf/final/consultations/imdrf-cons-samd-ce.pdf)
[49] National Institute For Health And Care Excellence (NICE). (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/evidence-standards-framework/digital-evidence-standards-framework.pdf)
[50] "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations. IMDRF (2014) (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf)
[51] Liu, X., Cruz Rivera, S., Moher, D. *et al.* Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. *Nat Med* **26,** 1364–1374 (2020). https://doi.org/10.1038/s41591-020-1034-x
[52] Topol, E. (2020). Welcoming new guidelines for AI clinical research. Nat. Med.

of these tools, their tendency to overfit on erroneous data features and produce unpredictable errors on unseen data features, and the lack of data from use in real world settings with long term results. Regulators and developers may determine that a tapered approach to post marketing monitoring and evaluation is appropriate in certain settings.

- ***Changes to the AI tool***

An update of an AI tool, by a code change, change of the user interface, or provision of further training data may alter the analytical or clinical performance of an AI tool. The group are not aware of currently approved medical AI solutions that are 'continuously learning' but anticipate that these may be developed. Taking checkpoints at regular intervals enables regular evaluation. Depending on the risk of the tool and the extent of the changes, the appropriate validation must be agreed by the developer and the regulator. Analytical validation against previously unseen datasets- or benchmarking against approved datasets representative of the intended setting or population could be useful in this scenario.

- ***Low- and middle-income countries***

There is considerable variation in the experience of international regulatory bodies with AI tools. Some countries also lack a dedicated national regulatory body. The WG-RC meetings have provided a forum for the sharing of expertise and discussion of common problems, including regulatory bodies and other interested stakeholders, some with aligned remits. Furthermore, there are important regulatory considerations related to the intended use and analytical and clinical validation of AI solutions in health. First, in low- and middle-income countries, one of the potential uses of AI solutions is in bringing specialized tools or knowledge to areas which do not have the relevant medical specialist (for example interpreting retinal scans, histopathology slides or radiology images). In high income countries, tools are more often positioned as an adjunct to medical professionals. Leveraging the evaluation performed to support regulation in a high income setting to inform how such tools are used in low- or middle-income settings therefore may not be appropriate. However, the full context of healthcare infrastructure and resources should be considered. Second, some regulatory bodies rely on decisions from other bodies to support their regulatory work. Given that the performance of AI solutions may be highly context dependent, additional steps may be required. The availability of a range of representative datasets would support local or national analytical validation. Finally, health AI solutions can be highly sensitive to shifts in data distribution and features. They may therefore be sensitive to differences in disease prevalence when moving from high to low-income counties, with the possibility of lower performance without appropriate evaluation or tuning with local data.

- **Data Quality**

  - ***Data in current health ecosystems***

The health sector has been very receptive to the benefits of AI thanks to the explosion of data and accessibility to computational power. Data is the most important ingredient for training AI/ML algorithms , and can be classified based on format, structure, volume, and many other factors. It can take any form, including: character, text, words, numbers, pictures, sound, or video. Also, each piece of data can be either structured, semi-structured, or unstructured. Structured data is normally stored in databases that are structured in a manner that follows a specific model or scheme such as data stored in electronic medical records, mobile devices, and Internet of Things (IoT) devices. While unstructured data refers to everything else that does not follow any particular model or scheme. Finally, data can be small, big, or metadata when it comes to volume expression. Nevertheless, regardless of the format, structure, volume of the data, a more general classification can be based on

**Commented [MR72]:** There is a question of whether such post market safety monitoring will be carried out. As per this study of drugs: https://www.nejm.org/doi/full/10.1056/NEJMp1705800 - only half have been completed and one fifth not even initiated.

**Commented [OMP73R72]:** That is a different context where compliance and other aspects are at play. I think from a conceptual pint of view, this is appropriate.

**Commented [L(74R72]:** Agree

**Commented [MR75]:** Are there certain applications of AI for which continuous learning may be too risky?

**Commented [OMP76R75]:** Could be, but that will be a risk-benefit evaluation that will vary drastically. I think the language is reasonable.

**Commented [MR77]:** There is a separate issue of whether most developers will even bother to ensure that AI technologies are adapted to LMICs, and thus whether regulatory agencies in HICs should require such adaptive studies to ensure wider use in LMICs, or carrots/incentives to encourage such additional development, testing, and validation.

**Commented [li78]:** Healthcare

**Commented [MR79]:** Not sure these are the right words?

**Commented [SA80R79]:** Thank you but bigdata is a common term to reflect the volume

the following 10Vs[53] (as illustrated in Figure 12 below): Volume, Veracity, Validity, Vocabulary, Velocity, Vagueness, Variability, Venue, Variety, and Value.

Commented [KE/RP81]: There is a typo under the Velocity box in the figure. Change to "THE SPEED AT WHICH DATA ARE GENERATED"

Commented [SA82R81]: The typo in the photo is from original referenced source and cannot be corrected.

- ***Good quality data in health AI solutions***

All AI tasks and solutions use some form of data regardless of its characteristics to facilitate machines to learn, adapt, and improve of their learning. However, data quality greatly influences the success of such solutions' safety and effectiveness. Good quality data is an ambiguous definition that is open to misinterpretation. Therefore, gaining a good understanding of the datasets used from the 10Vs perspective (mentioned above) is crucial to assess data quality in AI solutions during development and even after. The section below highlights key challenges and considerations for all stakeholders, including developers and regulators when handling data in AI solutions in order to achieve good data quality.

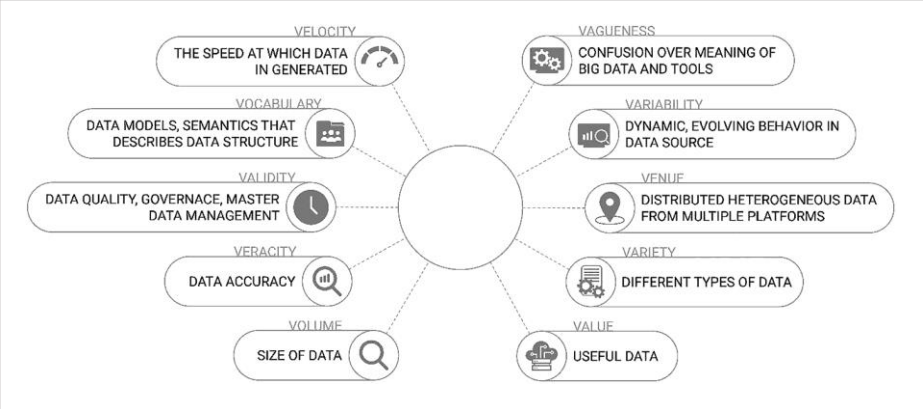


*Figure 11 The 10Vs of data[54].*

- ***Key quality data challenges and considerations for health AI solutions***

The availability of good quality datasets that are clinically relevant is one of the key challenges that developers face. However, data of varying quality can still be used depending on purpose, and thus, developers should determine if available data is of sufficient quality to support the development of systems that can achieve their intended goal. The lack of good quality datasets to be used in the development of AI solutions may hinder the effectiveness and potential benefits. Data that is not of sufficient quality for the intended purpose can also lead to many issues including, but not limited to, bias, datasets completeness, outliers, source device, traceability, integrity, and errors. In this section, some quality data issues that often arise when developing AI solutions and need to be considered by all stakeholders are discussed and summarized in Table 1. These issues and considerations can relate directly to dataset management, ML model, infrastructure used to manage the data, or general governance aspects:

Commented [OMP83]: What does this mean within this list? The list is strange ..bias and errors are bad, but the other items seems more like potential consideration. Consider rewriting

Commented [MR84]: These would seem to be the dimensions of poor (or adequate) data quality more than issues with data.

Commented [OMP85R84]: I provided suggested edits

- **Dataset management.** When managing datasets for ML models, a clear data management plan should be pre-specified and well-documented. Data management approaches should be

[53] Panesar A. (2019) Data. In: Machine Learning and AI for Healthcare. Apress, Berkeley, CA. https://doi.org/10.1007/978-1-4842-3799-1_2

[54] Ibid

risk based and fit for purpose. This may include, but is not limited to, data selection volume (including volume of data used and volume of available data), splitting, cleansing (including any AI algorithms that were used to clean the data), data usability (including how well the dataset is structured in a machine understandable form), labelling, dependencies, augmentation, and streaming. In addition, if data augmentation is relevant, it is important to develop a clear data augmentation strategy. Finally, in addition to the handling of the data, the capacity to plan for and conduct data analyses is also an important consideration.

- **Data inconsistency.** High heterogeneity in the syntax of the data requires harmonization in order to address issues related to multiple data sources with varying standards, formats, schemas, structures, and ambiguous semantics into a single coherent dataset for the purpose of its comprehensive analysis is especially challenging when using healthcare data. For example, much of the data collected from various information silos is inconsistent, incompatible, or not executable in machine-readable formats. For multiple data sources, there may be variations in how the data are captured (e.g., definitions of individual variables).
- **Dataset selection and curation.** Knowing the source of data and an initial assessment of the data quality can help to determine the potential for selection and information bias. Selection bias results when data used to produce the model are not fully representative of the actual data or environment that the model may receive or function in. In addition to selection bias, measurement bias is another relevant aspect that results when the data collection device causes the data to be systematically skewed in a particular direction. Therefore, developers should be aware of data quality limitations when attempting to curate and utilize these large-scale datasets. Moreover, developers and regulators need to know where the data originally came from and how it was collected and curated. This is especially important when the datasets are from an open-source database where the original source and specifications of the dataset may not be available. When the origin of data is difficult to establish, it would be prudent for developers to assess the risks of using such data and manage them accordingly. Finally, mitigation when having a heterogeneous dataset collected from a variety of reliable sources is also essential.
- **Data usability.** Knowing if the data used for development of the algorithm was intended for that training is essential, as developers need to convey their full understanding of the dataset and why it was suitable for their purpose. For example, data from a third-party source may be representative data intended for training purposes (e.g. case studies in tertiary education) and may not be suitable for training of an AI model intended to diagnose a disease or condition.
- **Data integrity.** Lack of data integrity is also important issue. This can be best understood by how well extraction and transformation have been performed on the dataset. To maintain data integrity, data verification checks may be developed. Data verification checks are a key component of data quality assurance when utilizing Real World Data for US FDA regulatory decision making. Data verification checks should also be the first step of data preparation for any ML workflow.

**Commented [pa86]:** We might want to explain what is meant by data integrity.

**Commented [lf87]:** https://healthpolicy.duke.edu/sites/default/files/2019-11/rwd_reliability.pdf

**Commented [SA88R87]:** Thank you.

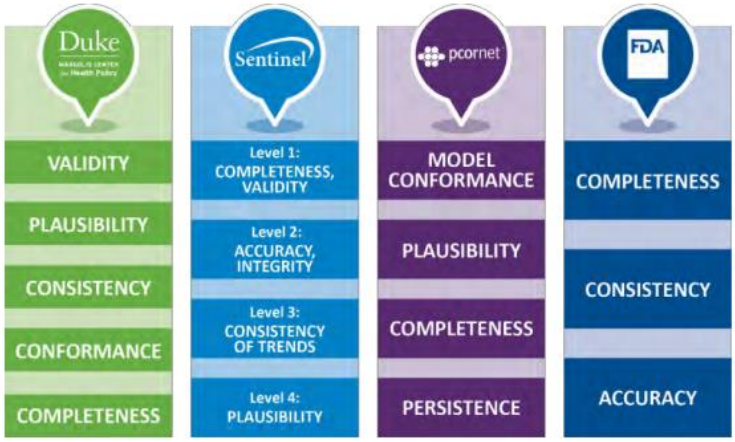


*Figure 12 Examples of quality check principles*[55].

- **Model Training.** AI-algorithms are usually trained on a separate dataset, named the training dataset and validated on a separate dataset, to reliably measure the performance of the algorithm. The training datasets should be well represented (for instance by considering prevalence of disease/condition) to avoid 'class imbalance'. Medical record data is inherently biased, and thus, there is a need to incorporate non-medical data such as the social determinants of health. Furthermore, underrepresentation of important diagnostic features may limit performance of the model and cause bias. This can be avoided by ensuring inclusion and exclusion criteria at the patient level and input data level do not create a selection bias. Furthermore, ensuring the datasets are reflective of the setting in which the model will be applied - a lack of diverse data (age, race, geographic areas) could limit the generalizability and accuracy of developed AI solution. This is demonstrated by a recent study by Stanford University[56] that shows 71% of patient data from just three states trains most AI diagnostic tools.
- **Data labelling.** It is important to ensure high quality Ground Truth labels of the training dataset. Subjective labelling and variability between labelers can introduce systematic and random errors.
- **Documentation and Transparency.** Often the algorithm and data supporting it are not available, or not well documented for all AI solution stakeholders. Therefore, this makes it difficult to assess the quality of the underlying data. Transparency and careful documentation are important not only on the methodology used in the collection of data, but also for the actual selection and modifications of datasets used for training, validation, and testing. Therefore, good documentation is fundamental to achieve transparency that would enable verification and traceability. Transparency of methods should ensure data quality. Beyond CONSORT-AI and SPIRIT-AI reporting guidelines already mentioned, specific checklists for reporting representativeness, completeness, and other data quality characteristics have been devised by the machine learning community[57,58]
- **Human factors**. It would be insufficient if data quality measures are implemented, unless the developers consider putting in place good data accountability practices for those handling the data

[55] https://healthpolicy.duke.edu/sites/default/files/2019-11/rwd_reliability.pdf
[56] Shana Lynch (2020). The Geographic Bias in Medical AI Tools. [Online] https://hai.stanford.edu/news/geographic-bias-medical-ai-tools.
[57] https://datanutrition.org/
[58] https://arxiv.org/abs/1803.09010

**Commented [MR89]:** I am guessing this refers to the United States so may be useful to contextualise a bit more.

**Commented [lf90]:** Cite: https://datanutrition.org/ https://arxiv.org/abs/1803.09010

**Commented [OMP91R90]:** Agreed – clarity needed

**Commented [SA92R90]:** Thank you this is very helpful.

**Commented [pa93]:** Suggest explaining what is meant by "human factors" here. Typically when HF is mentioned in a regulatory document, it is referring to usability (font size, button size, workflow design, etc.)

to ensure quality and integrity of data is maintained throughout the lineage of data. This is also essential for knowledge management and transfer in a highly evolving field.

Eventually, developers should consider deploying rigorous pre-release trials for AI solutions to ensure that they will not amplify any of the issues discussed above like biases and errors due to any issues with the training data, algorithms, or other elements of system design. Furthermore, careful design or prompt troubleshooting can help identify data quality issues early on. This could potentially prevent or ameliorate possible resulting harm. Finally, to mitigate data quality issues that arise in healthcare data and the associated risks, stakeholders should continue to work to create data ecosystems to facilitate the sharing of good-quality data sources.

**Commented [MR94]:** Should this be something that regulatory agencies require? Above there is a discussion of randomised trials being useful at least some of the time.

Below is a classified list that summarizes the key data quality considerations for AI solutions' safety and effectiveness[59]:

[59] This list will be updated and harmonized with IMDRF work.

*Table 3 General data quality considerations.*

| Category | Data quality consideration item |
|---|---|
| **Dataset** | Splitting |
| | Selection volume and size |
| | Selection bias |
| | Individual variables definitions in each dataset |
| | Raw data vs “cleaned” data |
| | Data wrangling and cleansing |
| | Parameters and hyperparameters |
| | Usability |
| | Characterization |
| | Labelling |
| | Dependencies |
| | Augmentation |
| | Manipulation |
| | Streaming |
| | Interfaces |
| | Integrity |
| | Unique requirements |
| | Data source |
| **Data Infrastructure** | Storage size |
| | Storage format |
| | Transformation medium |
| **AI/ ML Model** | Data Training |
| | Tuning Data |
| | Verification set |
| | Validation set |
| | Testing |
| | Development set |
| | Static AI vs dynamic AI |
| | Open AI vs closed AI |
| **Governance Management** | Liability |
| | Data access |
| | Risk Management |
| | Data Protection |
| | Privacy |
| | Adoption education for clinical practice |
| | Good practices |
| | Standards (of care, governance, interoperability, etc.) |
| | Scope of practice and AI model use |
| | Technical checklist |
| | Documentation |

| | |
|---|---|
| | Transparency |

- **Privacy and Data Protection**

The use of AI solutions and technologies for therapeutic development and healthcare applications presents considerable opportunities to advance medicine. However, there are a number of scientific, social, and ethical challenges related to potential health risks involved, equitable access, privacy, appropriate uses and users of AI technologies, bias, and inclusiveness. Stakeholders should carefully consider the potential issues that may arise in the development and use of their AI solution, as well as how such systems can align with established ethical frameworks and scientific standards in medical research and clinical care.

**Commented [MR95]:** This could probably be summarised a bit more precisely.

The WHO Global Strategy on Digital Health 2020–2025 classifies health data as sensitive personal data, or personally identifiable information, that requires a high safety and security standard. Therefore, it emphasizes the need for a strong legal and regulatory framework to protect the privacy, confidentiality, integrity, availability, and processing of personal health data. A responsive legal and regulatory framework can also address issues of cybersecurity, trust building, accountability and governance, ethics, equity, capacity building, and literacy. This will help ensure that good quality data are collected and subsequently shared to support planning, commissioning, and transformation of services.

To develop and maintain adequate data security strategies, it is important for AI solution developers, deployers, and manufacturers to understand the thickening web of privacy and data protections laws. This section discusses high-level considerations for privacy and data protection. For other ethical considerations, you may want to refer to the deliverable of the Working Group on Ethical Considerations on AI for Health[60].

- ***Current Landscape***

As the demand for health-related data increases, protecting privacy is creating a unique challenge for all stakeholders wishing to benefit from the many opportunities of AI technologies. One of the main reasons for this is that the high dimensionality of big data could make it difficult to apply anonymization and de-identification methods. Additionally, securing large-scale data sets against unauthorized access at each stage of the development process – collection, storage and management, transport, analysis, sharing, and destruction– is an important consideration.

Over 130 countries and regions have data protection regulations and privacy laws regulating the collection, use, disclosure, and security of personal information[61]. There are many different definitions and interpretations of "data protection" and "privacy." In some cases, data protection and privacy are used interchangeably. However, although these concepts are similar and often overlap, their meanings are different, and developers should be aware of the legal and ethical implications that result from these differences.

Laws and regulations that cover "the management of personal information" are typically grouped under "privacy policy" in the United States and under "protection policy" in the EU and elsewhere. These laws are often complex and may have conflicting obligations. When developing an AI solution for therapeutic development or healthcare applications, early in the development process developers

[60] For a broader discussion of privacy and other ethical considerations for the use of AI, refer to the deliverable of the FG-AI4H's Working Group on Ethical Considerations on AI for Health and international, regional, and national recommendations, such as the EU's Ethics Guidelines for Trustworthy AI (https://www.who.int/publications/i/item/9789240029200 ).

[61] Data Protection and Privacy Legislation Worldwide. United Nations Conference on Trade and Development (UNCTD). (2020) (https://unctad.org/en/Pages/DTL/STI_and_ICTs/ICT4D-Legislation/eCom-Data-Protection-Laws.aspx)

should consider gaining an understanding of applicable data protection regulations and privacy laws, including special regulatory provisions related to sensitive data, such as genetic data. Developers should also consider national, as well as regional laws. For example, in the United States, although the Health Insurance Portability and Accountability Act (HIPAA) sets a baseline for protecting health data, states are empowered to enact stricter privacy laws (e.g., California Consumer Privacy Act of 2018).

It is important to understand the jurisdictional scope of the various laws. For instance, because the scope of the GDPR is broad and its impact is significant, companies may want to at least consider the possibility and evaluate the extent to which they are subject to it. Most privacy laws, including the Singapore Personal Data Protection Act (PDPC), only apply to personal data processed within the country, whereas the GDPR[62] may apply to the personal data of European Union (EU) data subjects, regardless of jurisdiction.[63] As a result, companies subject themselves to compliance obligations under the GDPR if they are located in the EU (including if any component of that organization is located in the EU); offer goods and services to individuals located in the EU; or, monitor the behavior of individuals located in the EU.

It is also important for developers to understand the varied legal contexts and requirements for privacy-related concepts, such as "identifiable," "anonymous," and "consent." For example, some countries, like the UK, recognize episode level data as "identifiable" (whether it is de-identified/ pseudonymized, or not) and only aggregate data as "anonymous," while others like Australia have a more nuanced definition of "anonymous," which can include de-identified episode or person-level data. Moreover, various jurisdictions may require "explicit consent," with heightened information requirements for the processing of health-related data. Therefore, developers may want to consider the varied legal contexts when documenting how they address privacy-related concepts, including measures taken to meet consent requirements and the how they define anonymous or identifiable information.

In addition, certain jurisdictions have data protection regulatory frameworks that introduce reciprocity-based rules and place restrictions on the movement or transfer of data across borders. This might have a significant impact on the way in which data is processed and shared between countries. These provisions serve to curtail transnational data flows into and out of areas that are considered not to provide an "adequate" level of data protection.

Adequacy assessments may be required to determine if a recipient-country has thresholds of data protection laws and protections "essentially equivalent" or "substantially similar" to the jurisdiction from which the data was transferred. The GDPR, as a significant driver of emerging global data protection regimes, provides that the free transfer of personal data to third countries, non-European Union member states, can primarily occur where such third country is considered by the EU Commission as having an "adequate" level of protection[64]. To date, the EU Commission has only recognized 13 countries as providing adequate protection[65].

[62] See also India's proposed Personal Data Protection Act

[63] Like the GDPR, the CCPA applies to natural persons who are California residents who are "domiciled in the state or who is outside the state for a temporary or transitory purpose." Cal. Code Regs. tit. 18, §17014.

[64] Data flows have increasingly become an important part of global interconnection and AI development. Although the Schrems II case pertains to the EU-US position on data transfers, the wider implications inform global data transfers and the way it which they are to be compatible with GDPR requirements, including the validity of standard contractual clauses which depend on whether effective mechanisms are in place to ensure compliance with the level of protection required under the GDPR. *Data Protection Commissioner v. Facebook Ireland Limited, Maximillian Schrems* (Case C-311/18, "*Schrems II*").

[65] Adequacy decisions : How the EU determines if a non-EU country has an adequate level of data protection. European Commission (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/adequacy-decisions_en)

Therefore, developers should be aware of the nuances of the different jurisdictions regulations and laws and consider documenting their data protection practices accordingly. In general, companies should consider keeping current on new laws and requirements, leveraging governance, risk analysis, policies, trainings, and other strategies in a comprehensive and coherent way.

- ***Documentation and Transparency***

Documentation and transparency are critical to facilitate trust regarding privacy and data protection. Detailed privacy policy disclosures provide regulators with a benchmark by which to examine a company's data handling. These disclosures should identify significant uses of personal information for algorithmic decisions. Depending on the jurisdiction, the disclosures may require the inclusion of other relevant information, such as the types of health data collected and processed; the sources of the health data collected and processed; the identity of the persons or organizations which determined the purpose or means of processing personal data; the identity of the person or organization which processed the data; the legal bases for processing the data; how the data was collected, including whether adequate notice was provided to the data subject and how consent requirements were met; and, technical and organizational information concerning the storage of data, including security measures.

Developers should take privacy into account as they design and deploy AI solutions. This includes designing, implementing, and documenting approaches and methods to ensure a quality continuum across the development phases to protect data privacy[66]. Privacy protections should not just be limited to addressing cybersecurity risks, especially since some privacy risks can arise by means unrelated to cybersecurity incidents (e.g., harms to one's dignity, which may cause embarrassment or stigma, or more tangible harms, such as discrimination, economic loss, or physical harm)[67]. Therefore, when developing solutions to address risks, developers should have a general understanding of the different origins of cybersecurity and privacy risks and develop their risk management practices accordingly (see Figure 13 below[68]).

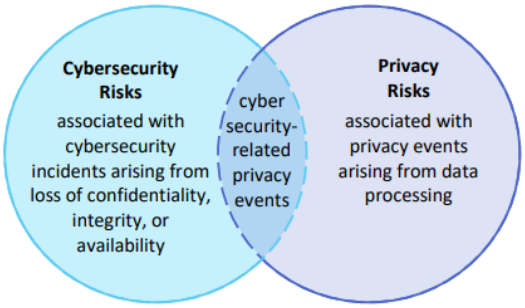


*Figure 13 NIST Privacy Framework – Cybersecurity and Privacy Risk Relationship.*

A compliance program should consider risks and develop privacy compliance priorities that take into account any specific potential harm, as well as the enforcement environment. Developers may want to consider including in their documentation a description of the operations involved in the processing

[66] For example, a pillar of the data quality continuum in some jurisdictions, e.g. EU law, is the accountability principle. According to Art. 5 of the GDPR, data controllers shall abide by the five sets of principles enshrined in Art. 5(1), e.g., data minimization. Data controllers shall determine both technical and organizational measures to attain such ends (Art. 5(2)), throughout the entire cycle of data processing. Although not mentioned, the accountability principle is also at work in Art. 24(1), 25(1), and 32 of the regulation in regard to the responsibility of the controller, principle of data protection by design (and by default), and security measures.
[67] NIST Privacy Framework: A Tool for Improving Privacy Through Enterprise Risk Management. NIST (2020). (https://www.nist.gov/system/files/documents/2020/01/16/NIST%20Privacy%20Framework_V1.0.pdf)
[68] Ibid.

of personal data, a risk assessment, and the measures implemented to mitigate risks that take into account the interests of data subjects.

Certain regulations outline prescriptive security requirements to address cybersecurity and privacy risks, such as the GDPR's data protection by design and default[69] and India's proposed data privacy by design policy[70], while others include the duty to implement and maintain reasonable security practices and procedures appropriate to the risk.[71] Privacy frameworks often include privacy impact assessments, which are a widely used privacy management tool to proactively evaluate and mitigate privacy risks. Some jurisdictions, including the EU [72], require companies to conduct these assessments[73]. Although the U.S. law does not require privacy impact assessments, the U.S. National Institute for Standards and Technology's (NIST) Privacy Framework recommends that developers conduct them. According to NIST, "identifying if data processing could create problems for individuals, even when an organization may be fully compliant with applicable laws or regulations, can help with ethical decision-making in system, product, and service design or deployment" [74]. This in turn can increase trust in the system.

Developers may also want to consider annotating their AI and having audit trails that explain what kinds of choices are made during the development process. Annotated notes provide "after the fact" transparency to outside parties and can help to explain the manner in which privacy was embedded, if applicable[75]. Such explanations and documentation should be at different levels of detail, targeted at different audiences – regulators, managers, developers, operators, and users. The nature of the information and explanations required may be different, but all of the assumptions, constraints, data sources, expected input and output, and major risks and limitations at each level should be clearly documented. In addition, an audit trail not only shows that controls have been applied, it could also potentially show how damage was mitigated in the case of a data breach.

Many jurisdictions enforce certain cybersecurity requirements or publish guidance on cybersecurity for developers of medical devices to consider. To provide transparency about cybersecurity practices, developers may want to consider documenting practices and approaches for data security, including policies that help protect the confidentiality, integrity, and availability of personal data throughout its lifecycle, such as appropriate encryption, access controls, logging methods, risk monitoring, and

[69] GDPR Articles 25 and 32.
[70] India's Personal Data Protection Act Ch. VI, 22(1)(e), 24(1).
[71] CCCPA § 1798.150(a)(1), South Africa's Protection of Personal Information Act of 2013, Israeli Privacy Protection Regulations (Data Security), 5777-2017 (implementing the Protection of Privacy Law, 5741-1981 of 1981), United Arab Emirates' Federal Law No. 2 of 2019, Kingdom of Saudi Arabia's E-Commerce Law of 2019 and its Implementing Rules.
[72] See Article 35, "A data protection impact assessment shall be conducted if processing is likely to result in high risk to the rights and freedoms of the natural persons."
[73] While risk assessments are quite common in information security standards and requirements, they are rarely seen in privacy rules in the U.S. The GDPR, however, requires that an organization processing personal data has to conduct a specific Data Privacy Impact Assessment or DPIA before beginning the processing.
[74] The NIST framework is a general guidance for data security and is not specific to health care data. NIST Privacy Framework: A Tool for Improving Privacy Through Enterprise Risk Management. NIST (2020). (https://www.nist.gov/system/files/documents/2020/01/16/NIST%20Privacy%20Framework_V1.0.pdf)
[75] West, Darrell M., and John R. Allen. *Turning Point: Policymaking in the Era of Artificial Intelligence*. Brookings Institution Press, 2020, 183.

methods of secure destruction. Developers may also consider documenting systems and approaches used to protect against data manipulation and adversarial attacks[76].

- **Engagement & Collaboration**

Separately, the fields of AI and ML and health—with different methods of communication (e.g., terminologies) and stakeholders—have their own approaches to engagement and collaboration. Through the development of new (or the modification of existing) AI solutions for health, these two fields converge. Consequently, engagement and collaboration, where applicable and appropriate, among AI and ML developers and manufacturers, healthcare practitioners and policymakers, regulatory bodies, and other stakeholders become necessary and, oftentimes, beneficial for the quality of the final product.

This section focuses on the engagement and collaboration approach of regulatory bodies with stakeholders in the area of AI and ML and health. First, we select a series of regulatory bodies, including the FDA, South African Health Products Regulatory Authority (SAHPRA), UK Medicines and Healthcare Products Regulatory Agency (MHRA), European Commission (EC), and Singapore Health Sciences Authority (HSA) and outline their approaches in table form. We clarify with whom, why, and how they foster engagement and collaboration. Then, we review the content of the tables (also referencing the supplementary literature provided at the end of the section), highlighting the most common traits (or noteworthy divergences) in the approaches.

We then reflect on two real-life examples of engagement and communication between regulators and AI developers resulting in positive clinical outcomes (CURATE.AI and IDentif.AI). In the last subsections, we offer thoughts on practical implications for resource-limited settings, we discuss the legal considerations that should be made by regulatory bodies in the context of engagement and collaboration, and we recommend ways that regulatory bodies in countries without past experience in engagement and collaboration can initiate this process. This is supplemented by several narratives: how to apply engagement tools (based on experience) and how to position the regulator as a partner in the context of accessible dialogue, guidance and recommendations ~~in~~during the ~~–~~development process.

- ***Approaches of regulatory bodies: a series of examples***

*Table 4. Engagement and collaboration strategy of FDA.*

| Organization (Country) | With whom? | Why? | How? |
|---|---|---|---|
| FDA (United States) | • Media (e.g., trade press); consumers; health providers, professionals, and | • To respond to requests related to FDA authority[81]<br>• To create mutual | • Patient outreach Newsroom and MedWatch[91]<br>• Public and private |

[76] The NIST Cybersecurity Framework is an internationally recognized document that explores these concepts in more detail. Framework for Improving Critical Infrastructure Cybersecurity. NIST (2018) (https://www.nist.gov/cyberframework )

[81] FDA Public Affairs Specialists, USFDA (2020). (https://www.fda.gov/about-fda/contact-ora/fda-public-affairs-specialists)

[91] FDA Track: Office of External Affairs USFDA (2021). (https://www.fda.gov/about-fda/fda-track-agency-wide-program-performance/fda-track-office-external-affairs)



**Commented [SA96]:** All references in this section has to be reformatted with author, title, year, and link (example: Nist Privacy Framework: A Tool For Improving Privacy Through Enterprise Risk Management. NIST (2020)(https://www.nist.gov/system/files/documents/2020/01/16/NIST%20Privacy%20Framework_V1.0.pdf))

**Commented [DH97R96]:** For links to Division webpages, added the division name, and forr the year, used the information provided in terms of Information current as of (Year). If this should be changed pls let me know and will edit. Thanks!

**Commented [ka98]:** Should these be grouped together as per the above sections?

**Commented [MR99]:** Although models of coregulation can be useful, it may also be important to note the importance of where the line is drawn between coregulation and codevelopment and regulatory oversight for which regulatory authorities need to have standalone authority that is independent of the developer. Perhaps this is clear earlier in document...

**Commented [ug100R99]:** The co-regulatory line is drawn by the set of goals to be achieved, and the principles and rights to be protected, according to the lawmaker. See e.g. Art. 5(1) of the GDPR. On this basis, the framework is set for multiple ways of engagement and collaboration (e.g. codevelopment). The troubles with AI depend on the fact that we're still debating what principles AI should have and abide by, although there's a certain consensus on guidelines and recommendations.

**Commented [MR101]:** Do we see regulators as 'partners' or as regulators? Not sure they can do both.

**Commented [DH102R101]:** Thanks for the comment. Added some clarification to mention partner in the sense of accessibility to guidances and recommendations/dialogue during the development process. Pls feel free to edit further.

**Formatted:** Centered, Keep with next

| | | | |
|---|---|---|---|
| | educators; and patients, patient advocates[77]<br>• Academia/industry[78]<br>• Government bodies and Congress[79]<br>• Foreign governments[80] | learning opportunities and knowledge exchange for promoting and protecting public health[82]<br>• To acquire reviews and contributions to reports, learn about advancements, and inform the field about policies[83]<br>• To learn about and contribute to scientific and technical advancements [84]<br>• To develop and inform the field about impactful policies[85]<br>• To protect and promote public health[86]<br>• Collaborate with | partnerships[92]<br>• ~~Research collaborations~~<br>• Training modules and education programs[93]<br>• Collaborative research projects through partnerships and research collaboration agreements [94]<br>• Enabling networking among experts (e.g., regulatory associations, patient advocacy groups)<br>• Workshops[95]<br>• Diversification of staff[96] |

**Commented [DH107]:** Probable duplicate

**Commented [DH103]:** Link doesn't work. I entered doc ID and see 21st Century Cures Act page but no document. Confirming this is correct thanks!

**Commented [DH104]:** Appears to be same document mentioned in footnote 83 (see note above)

[77] Office of External Affairs, USFDA (2018). (https://www.fda.gov/about-fda/office-commissioner/office-external-affairs); ; and https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-office-communications https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-division-public-education-and-outreach; and https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-office-communications

[78] CDER Division of Drug Information, USFDA (2021), (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-division-drug-information)

[79] FDA Public Affairs Specialists, USFDA, (2020). (https://www.fda.gov/about-fda/contact-ora/fda-public-affairs-specialists); Office of External Affairs, USFDA (2018). (https://www.fda.gov/about-fda/office-commissioner/office-external-affairs);FTC Releases New Guidance For Developers of Mobile Health Apps, US FTC, (2016). (https://www.ftc.gov/news-events/press-releases/2016/04/ftc-releases-new-guidance-developers-mobile-health-apps)

[80] International Programs, USFDA (https://www.fda.gov/international-programs)

[82] Partnerships: Enhancing Science Through Collaborations With FDA, USFDA (2020). (https://www.fda.gov/about-fda/partnerships-enhancing-science-through-collaborations-fda)

[83]https://www.regulations.gov/contentStreamer?documentId=FDA-2018-N-1910-0024&attachmentNumber=1&contentType=pdf

[84] Scientific Public Private Partnerships and Consortia, (2021). (https://www.fda.gov/drugs/science-and-research-drugs/scientific-public-private-partnerships-and-consortia)

[85]https://www.regulations.gov/contentStreamer?documentId=FDA-2018-N-1910-0024&attachmentNumber=1&contentType=pdf

[86] CDER Office of Communications, USFDA (2020). (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-office-communications)

[92] Scientific Public Private Partnerships and Consortia, USFDA (2021). (https://www.fda.gov/drugs/science-and-research-drugs/scientific-public-private-partnerships-and-consortia)

[93] Communications and Outreach, USFDA (2021) (https://www.fda.gov/federal-state-local-tribal-and-territorial-officials/communications-outreach)

[94] Centers of Excellence in Regulatory Science and Innovation (CERSIs), USFDA (2019) (https://www.fda.gov/science-research/advancing-regulatory-science/centers-excellence-regulatory-science-and-innovation-cersis)

[95]Public Workshop – Evolving Role of Artificial Intelligence in Radiological Imaging, USFDA, (2020) (https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/public-workshop-evolving-role-artificial-intelligence-radiological-imaging-02252020-02262020)

[96] Digital Health Advisor Job Description, USFDA (2020). (https://www.fda.gov/media/117300/download)

| | | | |
|---|---|---|---|
| | | government agencies to expand health IT efforts, interoperability of data to establish strong connections among stakeholders for advancing scientific, technical and regulatory framework[87]<br>• Alignment[88]<br>• Mutual assessments and sharing lessons learned[89]<br>• Harmonizing best practices and guidance documents[90] | • Digital and print media and graphics[97] |

*Table 5 Engagement and collaboration strategy of SAHPRA*

| Organization (Country) | With whom? | Why? | How? |
|---|---|---|---|

[87] (https://www.nitrd.gov/nitrdgroups/index.php?title=Medical-Device-Interoperability-2019; Multiple Function Device Products: Policy and Considerations, USFDA (2020). (https://www.fda.gov/media/112671/download
[88] International Regulatory Harmonization, USFDA (2020). (https://www.fda.gov/drugs/cder-international-program/international-regulatory-harmonization)
[89] International Agreements and Information Sharing, USFDA (2020). (https://www.fda.gov/drugs/cder-international-program/international-agreements-information-sharing)
[90] International Regulatory Harmonization ,USFDA (2020). (https://www.fda.gov/drugs/cder-international-program/international-regulatory-harmonization)

[97] CDER Division of Digital and Online Communications (2020). (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-division-digital-and-online-communications).



**Commented [RP108]:** There is something wrong with the numbering of the footnotes. This is not the correct number. I noticed this problem before I added footnotes.

**Commented [DH105]:** Possible duplicate with 78, or new reference?

**Commented [DH106]:** Duplicate of 88?

**Formatted:** Centered, Keep with next

| | | | |
|---|---|---|---|
| SAHPRA (South Africa) | • Industry (Manufacturers/ Distributors)<br>• Academia<br>• National department of Health<br>• National department of Trade & Industry<br>• Patients<br>• Clinicians<br>• Health technology assessments groups<br>• Trade associations<br>• Conformity assessment bodies<br>• South African National Accreditation Service | • Facilitate the approval of innovative AI solutions<br>• South African National Accreditation System (SANAS) to ensure Conformity Assessment Body network is established in country to certify quality management system (QMS) | • The framework for engagement and collaboration has not yet been formalized<br>• Recommended that stakeholder engagement adopt the five-step engagement model developed by the Therapeutic Goods Administration (TGA) Australia[98] |

*Table 6 Engagement and collaboration strategy of MHRA. Please note that several other bodies support the regulation of AI-based medical devices in the United Kingdom (e.g., Care Quality Commission, General Medical Council, and Health Research Authority). We have elected to focus our attention on the most prominent—MHRA—for this table.*

| Organization (Country) | With whom? | Why? | How? |
|---|---|---|---|
| Medicines and Healthcare Products Regulatory Agency (United Kingdom)[99] | • Healthcare professionals and providers in the National Health Service (NHS) and in private healthcare providers<br>• Media<br>• Patients, patient advocates; academia; medical device and in vitro diagnostic industry; health tech industry sector; | • Alert users to problems with medical devices and medicines<br>• Answer enquiries about role in regulation or raise awareness of safety issues<br>• Seek feedback on development of regulatory policy, managing adverse incidents and risks<br>• Interface with UK | • Central alerting system to the NHS and healthcare providers or through professional groups<br>• Media, public, and other stakeholder inquiries via MHRA Customer Service Centre, dedicated email |

[98] Australia Government Department of Health, Stakeholder Engagement Framework, AccountAbility. AA1000SE Stakeholder Engagement Practitioner's Perspectives (2005).

[99] Medicines and Healthcare Products Regulatory Agency; https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency



Formatted: Centered, Keep with next

Commented [M(109]: Move this as a note at the bottom of the table, or as a commentary in the main text.

Commented [AS110R109]: Dean, I will leave this to you.

Commented [DH111R109]: Can leave here as more visible. Thanks!

| | | | |
|---|---|---|---|
| | consumers/general public<br>• Domestic government bodies including Department of Health and Social Care (DHSC), NHS Digital, NHSX, National Institute for Health and Care Excellence (NICE), and Care Quality Commission (CQC) | government and NHS including stakeholders aligned to digital and AI-related activities | inboxes, and Press Office<br>• Connecting with Expert Advisory Groups, networks, and stakeholder groups on specific issues<br>• Consultation on engagement with patients and public[100]<br>• Working-level meetings with national stakeholders, bilateral meetings with other parts of NHS, government and international counterparts |

*Table 7 . Engagement and collaboration strategy of EC*

| Organization (Country) | With whom? | Why? | How? |
|---|---|---|---|
| European Commission (EC)[101] | • "All umbrella organisations/ associations with a European outreach, representing the following sectors/groups: the health tech industry, patients, healthcare professionals and the research community." | • To "support the Commission in the development of actions for the digital transformation of health and care in the EU." | • By providing "advice and expertise to the Commission, particularly on topics set out in the communication[102] on enabling the digital transformation of health and care in the Digital Single Market, that was adopted in April 2018." In particular, such topics regard health data |

**[100]** How should we engage and involve patients and the public in our work, MHRA (2020) (https://www.gov.uk/government/consultations/how-should-we-engage-and-involve-patients-and-the-public-in-our-work)

[101] EU ehealth stakeholder group initiative, European Commission (2020) (https://ec.europa.eu/digital-single-market/en/news/ehealth-stakeholder-group-relaunched)

**[102]** Communication on enabling the digital transformation of health and care in the Digital Single Market; empowering citizens and building a healthier society, European Commission (2018) (https://ec.europa.eu/digital-single-market/en/news/communication-enabling-digital-transformation-health-and-care-digital-single-market-empowering)



Formatted: Centered, Keep with next

Commented [KM112]: Should this footnote be moved to the end of this quote?

Commented [AS113R112]: Dean I will leave that to you to decide.

Commented [DH114R112]: Yes thanks Monique and Shada. I tried to move to the end but the footnote wasn't accessible at this point.

| | | | |
|---|---|---|---|
| | | | interoperability and record exchange formats, digital health services, data protection and privacy, AI, and "other cross cutting aspects linked to the digital transformation of health and care, such as financing and investment proposals and enabling technologies." |

*Table 8 Engagement and collaboration strategy of HSA.*

| Organization (Country) | With whom? | Why? | How? |
|---|---|---|---|
| Health Sciences Authority (Singapore)[103, 104] | • Ecosystem stakeholders and innovators (universities, research institutes, startups, etc.) who are addressing the use of technologies such as AI, Internet of Things (IoT), and related platforms for health/medicine<br>• Manufacturers, software and AI developers. Industry and Trade Associations<br>• Other government agencies responsible for deployment of technologies in healthcare system, healthcare professionals, and professional groups, healthcare institutions,<br>• | • Early engagement and support to innovators to facilitate regulatory compliance thus facilitating timely access to safe innovations for patients<br>• Actively consult on new policies and guidelines related to AI and software medical devices to receive and incorporate stakeholders' inputs and perspectives Regulatory Guidelines for Software Medical Devices – A Life | • Rapid, streamlined engagement portals are available for several facets of product regulation[106]<br>• Specific processes that can be straightforwardly addressed include ~~Pharmaceutical Regulatory Information System (PRISM) and~~ Medical Device Information Communication System (for application submissions for licenses, permits, registrations, etc.)<br>• ~~Obtaining a CRM N is often required for submission of a clinical validation~~ |

[103]Health Sciences Authority, Singapore, (www.hsa.gov.sg)
[104] Health Sciences Authority, Singapore, HSA (www.hsa.gov.sg)
[106] E-services, HSA (2021) (https://www.hsa.gov.sg/e-services)



**Formatted:** No widow/orphan control

**Commented [li115]:** Remove footnote 105 on Special Authorisation route. Replace 104 with www.hsa.gov.sg. which direct reader to the main landing page.

**Commented [DH116R115]:** Thanks very much. The edit has been made, and 105 will be removed per recommendation.

**Formatted:** List Paragraph, Outline numbered + Level: 1 + Numbering Style: Bullet + Aligned at: 0 cm + Indent at: 0.63 cm, No widow/orphan control

| | | | |
|---|---|---|---|
| | | Cycle Approach[105]<br>● To work with other agencies responsible for implementation and deployment of AI and software medical devices in healthcare system to facilitate greater adoption of innovative technologies in the healthcare system<br>● | ~~programme as it stipulates a prerequisite of an initial assessment of device risk from the HSA~~<br>● Online self-help tools to determine the product classification and risk classification for medical devices and simple forms to seek advice and confirmation from the HSA[1]<br>● **Medical Device Development Consultation**: Online appointment booking system that allows innovators and developers to seek scientific and regulatory advice during medical device development phase to facilitate regulatory compliance<br>● Online stakeholder consultation process for all new and revised policies and guidelines<br>● Regular focus group discussions and engagements with industry associations and companies<br>● |

**Commented [DH117]:** Becomes footnote 105

**Formatted:** List Paragraph, Bulleted + Level: 1 + Aligned at: 0.63 cm + Indent at: 1.27 cm

**Commented [li118]:** footnote: https://crm.hsa.gov.sg/Webform/HPRG

**Commented [DH119R118]:** Thanks very much. Will become footnote 106 with following text:
Health Product Classification Form, HSA (2019), (https://crm.hsa.gov.sg/Webform/HPRG)

**Commented [DH120R118]:** Please confirm if 2019 is OK to use (based on date noted at bottom of webpage).

**Commented [DH121]:** Becomes footnote 106

**Formatted:** Normal, No bullets or numbering

[105]Regulatory Guidelines for Software Medical Devices – A Life Cycle Approach, HSA (2020)( HYPERLINK "https://www.hsa.gov.sg/docs/default-source/hprg-mdb/gudiance-documents-for-medical-devices/regulatory-guidelines-for-software-medical-devices---a-life-cycle-approach.pdf"https://www.hsa.gov.sg/docs/default-source/hprg-mdb/gudiance-documents-for-medical-devices/regulatory-guidelines-for-software-medical-devices---a-life-cycle-approach.pdf)

- ***Discussion about strategies of profiled regulatory bodies***

Within the series of tables, we find the approaches of four national bodies and one multinational (in the case of EC) regulatory body to foster engagement and collaboration. In the first category ("with whom"), there are considerable similarities among these bodies. The shared targets for engagement and collaboration include health professionals (indicated by FDA, SAHPRA, MHRA, and EC), academia (FDA, SAHPRA, MHRA, EC, and HSA), industry (FDA, SAHPRA, MHRA, EC, and HSA), patients or patient advocates (FDA, SAHPRA, MHRA, and EC), domestic government bodies (FDA, SAHPRA, and MHRA), media (national and trade press; FDA and MHRA), health providers (FDA and MHRA), and consumers (FDA and MHRA). Interestingly, the strategy paper by the National Institute of Standards and Technology (NIST)—provided under "Additional sources of relevant literature" at the end of this section—also refers to academia and domestic government bodies as targets for engagement and collaboration.

In the second category ("why"), SAHPRA mentions the importance of communicating the benefits and intended use of devices, presumably to protect and promote public health (listed by FDA and implied by MHRA). FDA also stresses the importance of bilateral communication with stakeholders so that regulators are aware about developments in industry (or academia) and so that these stakeholders, in turn, are aware about developments in regulation. Similarly, MHRA indicates the importance of acquiring feedback about medical devices from stakeholders. This supports the objectives given by both SAHPRA and EC: to facilitate approval of innovative solutions and support the digital transformation of health and care. The Health Sciences Authority (HSA) acknowledges the importance of early engagement with the innovators and developers to provide greater clarity in regulatory requirements and improve transparency in regulatory processes.

For the third category ("how"), FDA lists steps that are taken to foster engagement (e.g., hosting workshops, producing digital and print material, and offering training modules or other types of education). MHRA also notes the importance of holding meetings with stakeholders (including domestic government institutes and international counterparts)~~HSA has developed a "Pharmaceutical Regulatory Information System" and "Medical Device Communication System," which recall the central alerting system of MHRA~~. HSA has introduced Pre-market Consultation Scheme to support innovation and device development by providing scientific and regulatory advice to enable regulatory compliance by software and AI developers, who unlike traditional medical device players are not familiar with regulatory requirements. [107][OBJ][108][109]

- ***Two successful instances of engagement***

To understand the value of engagement and collaboration among regulatory bodies and stakeholders, we provide two real-world examples (hereafter, Cases 1 and 2). Clear avenues for engagement between regulators and AI developers play a major role in ensuring that rigorous evaluation and accelerated delivery of impactful modalities can be seamlessly realized. One aspect is the area of interventional AI/digital medicine, which involves the application of software/devices (e.g., AI-based drug development and/or dosing platforms) and/or the application of resulting drug compounds

[107] Australia Government Department of Health, Stakeholder Engagement Framework, AccountAbility. AA1000SE Stakeholder Engagement Practitioner's Perspectives. 2005

[109] International Association for Public Participation (IAP2) Spectrum (2007)

and/or combinations recommended by these platforms[110,111,112]. In this context, integrating regulator accessibility with emerging innovation, sometimes under urgent circumstances, will ultimately result in life-saving outcomes. Importantly, these outcomes will not solely be confined to post-approval treatment, but to substantial patient benefit during the investigational stages of validation as well.

In Case 1, the developmental roadmap and validation of CURATE.AI and foundational technology of IDentif.AI was discussed with the Medical Devices Branch[113] of the Health Sciences Authority (HSA) in Singapore. This interactive session included an in-depth review of the key findings of the technology platforms, the process of implementing both platforms, emerging statistical analysis strategies to effectively assess personalized medicine treatment outcomes, and regulatory routes. A broader discussion pertaining to how clinical trial designs themselves may evolve due to the emergence of AI was also conducted.[114,115,116] A clear pathway for subsequent inquiries was established, as multiple and frequent guidance requests were expected due to the nature of the trial designs that were envisioned. These included *N*-of-1 study designs for a broad range of indications designed for each patient. Specifically, these designs were personalized based on (e.g.,) the individualized dosage calibrations of the drug regimen (clinician-selected regimen), serial efficacy and toxicity measurements, efficacy-guided treatment protocol, and safety parameters. Subsequent submissions have included engagement with regulators for risk classifications associated with the device for each trial and subsequent discussion for submission of special access routes (SARs) for the potential rapid implementation of *N*-of-1 trials and for treatment purposes if needed.[117] Rapid and informative responses and active engagement from HSA regulatory team members resulted in efficient turnaround times for trial initiation, which ultimately resulted in a positive outcome for a refractory oncology patient. A sustained track record of engagement with the regulatory community has played a key role in helping a clear process flow to be developed for downstream guidance requests.

Case 2 was developed in response to the COVID-19 pandemic. Specifically, a patient-derived live virus strain was harnessed for IDentif.AI-driven combination therapy optimization to serve as a clinical decision support system (CDSS). Contrary to traditional AI-based approaches, this strategy did not use pre-existing patient datasets. Instead, prospective experimentation was used alongside an AI-derived small data analytics strategy to pinpoint prospective data-backed rankings of combinations for potential further clinical consideration and potentially for the elimination of certain combinations from further clinical consideration. The foundational technology for IDentif.AI was

Commented [DH122]: Probable duplicate

[110] D. Ho, Artificial Intelligence in Cancer Therapy (2020) (https://science.sciencemag.org/content/367/6481/982)

[111] D. Ho, Addressing COVID-19 Drug Development with Artificial Intelligence (2020) (https://onlinelibrary.wiley.com/doi/full/10.1002/aisy.202000070)

[112] A. Blasiak, J.J. Lim, S.G.K. Seah, T. Kee, A. Remus, D.H. Chye, P.S. Wong, L. Hooi, A.T.L. Truong, N. Le, C.E.Z. Chan, R. Desai, X. Ding, B.J. Hanson, E.K.-H. Chow, D. Ho, IDentif.AI: Rapidly optimizing combination therapy design against severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) with digital drug development, (2020) (https://aiche.onlinelibrary.wiley.com/doi/10.1002/btm2.10196)

[113] Health Sciences Authority: Regulatory Guidelines for Software Medical Devices – A Lifecycle Approach; https://www.hsa.gov.sg/docs/default-source/announcements/regulatory-updates/regulatory-guidelines-for-software-medical-devices--a-lifecycle-approach.pdf

[114] D. Ho, S.R. Quake, E.R.B. McCabe, W.J. Chng, E.K. Chow, X. Ding, B.D. Gelb, G.S. Ginsburg, J. Hassenstab, C.M. Ho, W.C. Mobley, G.P. Nolan, S.T. Rosen, P. Tan, Y. Yen, and A. Zarrinpar, Enabling Technologies for Personalized and Precision Medicine (2020) (https://www.cell.com/trends/biotechnology/fulltext/S0167-7799(19)30316-6)

[115] P. Shah, F. Kendall, S. Khozin, R. Goosen, J. Hu, J. Laramie, M. Ringel, N. Schork, Artificial intelligence and machine learning in clinical development: a translational perspective Artificial intelligence and machine learning in clinical development: a translational perspective, (2019) (://www.nature.com/articles/s41746-019-0148-3)

[116] S. Harrer, P. Shah, B. Antony, J. Hu (2019) Artificial Intelligence for Clinical Trial Design; (https://www.sciencedirect.com/science/article/pii/S0165614719301300#:~:text=AI%20techniques%20have%20advanced%20to,to%20assist%20human%20decision%2Dmakers.&text=We%20explain%20how%20recent%20advances,towards%20increasing%20trial%20success%20rates)

[117] Special Access Route (Medical Devices), HSA (2019) (https://www.hsa.gov.sg/medical-devices/registration/special-access-routes/qualified-practitioner-request)

previously discussed in detail with the HSA Medical Devices Branch, and additional IDentif.AI SARS-CoV-2 study information was provided in the context of clinical decision support, developing optimized combinations pinpointed by IDentif.AI, and potential trials being designed with clinical partners. With regards to regulator engagement, the Medical Devices Branch of the HSA was contacted to provide device risk classification guidance for the submission of a Clinical Research Materials Notification (CRM-N) for study purposes. Obtaining a CRM-N is a required segment of the submission of a clinical validation program because it stipulates a prerequisite of an initial assessment of device risk from the HSA[118]. Of note, the submission portal and portal interaction were particularly straightforward to navigate and integrated with a uniform access portal, which was streamlined for efficient oversight and monitoring with regulatory bodies. This further demonstrates the straightforward process of interaction with the HSA. This case served as an example of the critical importance of straightforward regulator accessibility and the profoundly positive impact that this can have on the advancement of promising technologies towards further clinical assessment and validation.

- ***Comments about legal constraints***

As demonstrated by the previous use cases, good regulatory outcomes can depend on collaboration and engagement. It is clear that potential benefits are to be gained through increased collaboration and engagement with various actors and stakeholders. However, once it has been established "with whom" a regulator might want to collaborate and engage, it is necessary to determine "why" they might want, or need, to do so. Collaboration and engagement take varying forms across different countries and are underpinned by a range of legal and ethical requirements. These requirements may stipulate and describe conditions either enabling, or restricting, collaboration and engagement processes. Supporting frameworks for cooperation and collaboration, including information and work sharing, for instance, may rely on confidentiality arrangements and memoranda of understanding with regulatory bodies in other countries. Additional duties, obligations, or constraints may arise from international agreements, national legislation, other laws and regulations, various ethical instruments, policies and technical standards, and stakeholder engagement arrangements. Normative frameworks vary between countries, and regulators might have differing legal and ethical requirements and obligations (e.g., data protection requirements, issues of transparency and accountability) depending on a particular legal environment and the nature of the collaboration and engagement.[119] These should not necessarily be seen as a barrier to collaboration and engagement, but as an opportunity. Accordingly, it will be incumbent upon a regulator to consider any particular legal and ethical duties, obligations and requirements that might arise within their specific jurisdiction, and ensure they are adhered to, when fostering sound collaboration and engagement practices.

- ***Recommended approaches for countries without past experience***

For countries with limited experience in engagement and collaboration (and/or limited resources), several considerations should be made. For instance, what levels of engagement and collaboration are desired and what steps can and should be taken to achieve this? Also, what challenges are presented by this technology (e.g., AI explainability)?

In many cases, it is desirable to adopt regulatory models that are adaptable, flexible, modular, and scalable, to accommodate the uncertainties of innovation through appropriate forms of oversight and coordination. These features not only fit the specific challenges of emerging technologies, but also the regulatory approach of countries without past experience in this field, or with scarce economic resources. Priorities, on the one hand, should be scalable, so that growing amounts of work can be

**Commented [MR123]:** As per above, should these be spelled out more? The 'complexity' of some AI technologies (which should increase over time), much like derivatives in the financial sector or airplanes, could push regulators that are understaffed and underqualified to engage more in coregulatory approaches as a means of promoting innovation and understanding what they are regulating, but could also cross over some of the lines that should divide regulators from developers, especially in the field of health. These legal and ethical duties and constraints, while arguably different in this field, may be worth spelling out?

**Commented [ug124R123]:** Again, in a coregulatory approach, there's always a fundamental distinction between regulators and developers, because lawmakers establish the sets of principles, rights, goals, etc. that represent the general framework for any form of engagement, collaboration, etc.

**Commented [MR125]:** Or more generally, should countries not use such technologies until and unless they can properly regulate such technologies, or work with other countries or international institutions to ensure such technologies can be introduced with a certain level of QA and post approval oversight?

[118] **HEALTH PRODUCT CLASSIFICATION FORM** Health Product Classification Form, HSA) (https://crm.hsa.gov.sg/Webform/HPRG)

[119] B.A. Townsend, and D.W.Thaldar, DW (2019) Navigating uncharted waters: biobanks and informational privacy in South Africa, *South African Journal on Human Rights*, 35(4): 329-350. https://doi.org/10.1080/02587203.2020.1717366

suitably addressed by adding resources to the regulatory model. On the other hand, priorities should be determined in accordance with the modular adaptability of the steps and levels of engagement. In ecology, adaptability regards the ability to cope with unexpected disturbances in the environment. In engineering, modularity refers to the interrelation of the separate parts of a software package or also to the partitioning of the design to make it manageable. In multi-agent systems (MAS), it refers to the efficient usage of computational resources. We can profit from this notion to create adaptable policies that can be combined into regulatory systems for legal governance. The aim should be to address the uncertainties of innovation, aligning with society's preferences on emerging innovation, while allowing regulators to capture expanding understanding of technological challenges with increasing normative granularity.[120]

- ***Narrative on using engagement tools in practice based on practical experience of using them***

For all countries—from those with limited experience in engagement and collaboration (and/or limited resources) to those on the other end of these spectra—project and programme management tools can help organizations (including regulators) structure and execute their engagement with stakeholders and users. No matter which tool is chosen, the key to valuable engagement is investing the time, energy, and thought into how best to engage stakeholders and following through on that engagement for the duration of a project or program. Often, engagement fails if the investment is seen as a short- rather than long-term relationship.

The Australian Government's recommended five-step model for engagement[121] is a good starting point for considering how a regulator could engage with developers of AI health products and services. In this model, engagement starts with thinking through the purpose of engagement (based on what it is hoped to achieve) and identifying relevant stakeholders. When planning out the different levels of engagement with stakeholders, it is recommended to map out existing relationships and to define the type of engagement and relationship that is needed with the stakeholder (and what type of relationship they would be open to having). For example, a digital health developer building an app to support parents with children above a healthy weight may find the primary health body is an influential stakeholder because it sets policies around managing children's weight. However, it is not a body with whom the developer of the app needs to engage regularly, so the developer may only "inform" the health body of the project. Contrarily, a developer will want to work with parents of children above a healthy weight to co-design the app and ensure it fits their needs. It would, therefore, be important for the developer to "collaborate" with a representative group of parents and establish two-way/multi-way communication and shared learning and decision-making over the course of the project.

Another similar approach for making sure that stakeholders are provided with the right information at the right time and using the optimal communication channels is outlined by the leading product development software company Atlassian[122]. Within the stakeholder communication "play," importance is placed on who the stakeholders are, the desired method of communication, and the frequency of communication. For example, for an internal government project developing a digital health product, there will be internal stakeholders (like funders of the project and policy leads) and external stakeholders (like leading academics). The communications plan should outline how each stakeholder group will be addressed (email, face-to-face conversations, video call, and/or social

[120] Cf. Pagallo, U., Casanovas, P. and R. Madelin (2019) The Middle-out Approach: Assessing Models of Legal Governance in Data Protection, Artificial Intelligence, and the Web of Data, *The Theory and Practice of Legislation*, 7(1): 1-25.

[121] Australia Government Department of Health, Stakeholder Engagement Framework, AccountAbility. AA1000SE Stakeholder Engagement Practitioner's Perspectives,(2005) (https://www.health.gov.au/sites/default/files/stakeholder-engagement-framework_0.pdf)

[122] Stakeholder Communications, Atlassian (https://www.atlassian.com/team-playbook/plays/stakeholder-communications-plan)

media) and how often there were will be contact with the stakeholder group (daily, fortnightly, and/or yearly) based on what the relationship with the stakeholder brings to the overall goals (i.e., information sharing, co-design, and/or quality assurance). This plan can then be mapped out in a simple table (example headings: method, audience/stakeholder, content to share, why, and frequency) for the whole development team to follow.

- ***Narrative positioning the regulator as a partner in the development process***

As demonstrated in the tables and discussed in the subsequent text, multiple regulatory bodies emphasize the importance of open (bilateral) communication with stakeholders so that regulators are aware about developments in AI-based technology developments and so that these stakeholders, in turn, are aware about changes in regulation. This is because AI-based technology is constantly changing and regulation needs to be able to keep pace with its iterative nature. The development, deployment, post-market surveillance, and iteration of AI products and services in healthcare should, therefore, be an ongoing conversation between developers and regulators.

It is recommended that regulators look at AI-based technology in healthcare from a mindset of . accessible engagement that potentially, when applicable, enables working alongside the developer to ensure compliance with regulatory requirements throughout the development and implementation process. A engagement mindset approach to regulation is about building trusting, collaborative relationships between developers and the regulatory body(s) along with a two-way dialogue that enables developers to learn from regulators and vice/versa.

Furthermore, depending on a country's regulatory arrangements one or more regulators may be responsible for AI-based health products and services. This means a developer often has to work with (and meet the standards of) more than one regulatory body. To ensure that this is a smooth and positive experience for AI developers, it is again recommended that regulators take a service approach. By this, it is meant that a single, clearly marked pathway should be established to be followed by an AI developer when ensuring the compliance of a product or service. Regulators need to collaborate with each other on clear messaging to developers, consistent levels of engagement with developers at the right point, and sharing learnings about different engagements with developers.

If a country wants to take an accessible engagement ~~service~~ mindset approach to regulation of AI products and services one step further, co-regulation, could be explored. As outlined by Clark[123], with a coregulation approach regulators outlined a regulatory framework based on needed compliance to the legislative act(s) and the detail of how this is applied in practice is jointly developed by regulators and a representative sample of developers[124]. Similar to the above point about regulation from a service mindset, a co-regulatory approach is about generating buy-in from developers through engaging them in the design and implementation of the regulatory process. It is also about designing a regulatory process that reflects and acknowledges the needs of developers as well, not just those of the regulatory body and associated bodies. However, ultimately regulators must remain fully independent of developers to make decisions that put the public's safety first, as well as ensuring that public and private healthcare resources are only used for technologies that meet independently developed standards of quality, safety, and efficacy. While a developer and regulator should design a regulatory framework that is flexible and workable for both parties, this should not be confused with the necessity of regulators remaining independent and ultimately capable of making decisions without any undue influence by the entity that is being regulated.

**Commented [MR126]:** Just again raising a flag that a 'service mindset' for regulators with these technologies could be seen as excessively close/improper for some who may believe that while effective communication is needed to enable developers to produce useful technologies, there is still a need for arms-length regulation and oversight.

**Commented [DH127R126]:** This is helpful. Tried to clarify some. Please feel free to edit.

**Commented [MR128]:** What happens if a data protection authority views a technology as not meeting its standards while a health technology agency does? How do regulators collaborate with one another to ensure the best outcomes for patients can be achieved? (Had mentioned this above in the data protection section also).

**Commented [MR129]:** There are important ethical, legal, and historic reasons to question co-regulation, especially at a time of heightened sensitivity about such technologies, and the companies that develop and deploy such technologies (especially if there is an information asymmetry between the regulator and the company, in which coregulation may not allow a regulator to introduce effective oversight).

**Commented [MR130]:** This is just suggested language, not what should be used. I would hope there would be significant caution around how to discuss these issues, especially in light of recent concerns with regulatory independence, for example, with aducunamab. I realise drugs are not the same thing as AI technologies, but there is a heightened sensitivity to regulatory independence that this group should take into account.

[123] R. Clarke(2019). Regulatory alternatives for AI. Computer Law & Security Review. (https://doi.org/10.1016/j.clsr.2019.04.008)
[124] Ibid

# 6. Recommendations for the Way Forward

*Based on its work, the WG-RC recommends that stakeholders examine the key considerations discussed in Section 5 above and summarized in Table 9 below as they continue to develop frameworks and best practices for the use of AI in healthcare and therapeutic development. Table 9 List of key recommendations for regulatory considerations for AI in Health based on each of the 6 topic areas*

| Topic Area | Recommendation list |
|---|---|
| **1. Documentation and Transparency** | 1.1 Pre-specify and document the intended purpose and development process, such as the selection and use of datasets, parameters, metrics, deviations from original plans, and updates, during the phases of development should be considered in a manner that allows for the tracing of the development steps as appropriate. |
| | 1.2 Consider a risk-based approach for the level of documentation and record keeping utilized for the development and validation of AI solutions. |
| **2. Total Product Lifecycle Approach and Risk Management** | 2.1 Consider a holistic risk management approach that addresses risks associated with an AI medical device, such as cybersecurity threats and vulnerabilities, throughout all phases in the life of a medical device including pre-and post-market. |
| **3. Intended Use, and Analytical and Clinical Validation** | 3.1 Transparent documentation of the intended use of a tool including the setting and patient should be provided. Details of the training dataset composition underpinning an AI tool, including size, setting and population, input and output data and demographic composition should be transparently documented and provided to users. |
| | 3.2 External, analytical validation, in an independent dataset is required to demonstrate performance beyond the training data. This should be representative of the population and setting in which the tool is intended to be deployed, and transparent documentation of the external dataset and performance metrics should be provided. |
| | 3.3 For clinical validation a graded set of requirements based on risk is recommended. Randomized clinical trials are the gold standard for evaluation of comparative clinical performance and could be appropriate for the highest risk tools or where the highest standard of evidence is required. |
| | 3.4 Prospective validation is real world deployment and implementation trial which a relevant comparison group showing a meaningful improvement in outcomes using accepted endpoints may be appropriate for other risk classes. |
| | 3.5 A period of more intense post deployment monitoring for adverse events should be considered. Further consideration of this is being undertaken by the WG on clinical evaluation. |
| **4. Data Quality** | 4.1 Developers should determine if available data is of sufficient quality to support the development of systems that can achieve their intended goal. |

**Commented [PR131]:** What about quality management (e.g., making sure the device does not malfunction)?

| | |
|---|---|
| | 4.2 Developers should consider deploying rigorous pre-release trials for AI solutions to ensure that they will not amplify any of the issues discussed above like biases and errors due to any issues with the training data, algorithms, or other elements of system design. |
| | 4.3 Careful design or prompt troubleshooting can help identify data quality issues early on. This could potentially prevent or ameliorate possible resulting harm. Finally, to mitigate data quality issues that arise in healthcare data and the associated risks, stakeholders should continue to work to create data ecosystems to facilitate the sharing of good-quality data sources. |
| 5. **Privacy and Data Protection** | 5.1 Privacy and data protection should be considered during the design and deployment of AI solutions. |
| | 5.2 Early in the development process, developers should gain an understanding of applicable data protection regulations and privacy laws. |
| | 5.3 A compliance program should address risks and develop privacy and cybersecurity practices and priorities that take into account potential harm, as well as the enforcement environment |
| **6. Engagement and Collaboration** | 6.1 It is important to consider the development of accessible and informative platforms that facilitate engagement and collaboration, where applicable and appropriate, among key stakeholders of the AI innovation and deployment roadmap. These include but not limited to AI/ML developers, device manufacturers, healthcare practitioners, policymakers, and regulatory bodies. These engagement and collaboration platforms may play a key role in streamlining the oversight process for AI regulation while also accelerating practice-changing advances in AI to the user community. |

# 7. Conclusion

The WHO recognizes the potential of Artificial Intelligence (AI) in enhancing health outcomes by improving medical diagnosis, digital therapeutics, clinical trials, self-management of care and person-centered care, as well as creating more evidence-based knowledge, skills and competence for professionals to support health care. Furthermore, with the increasing availability of healthcare data and the rapid progress of analytics techniques, AI has the potential to transform the health sector to meet a variety of stakeholders' needs in healthcare and therapeutic development. For this reason, the WHO and ITU are collaborating through the Focus Group on AI for Health (FG-AI4H) to facilitate the safe and appropriate development and use of AI solutions in healthcare FG-AI4H's Working Group on Regulatory Considerations (WG-RC) on AI for Health consists of members representing multiple stakeholders including regulatory bodies, policy makers, academia, and industry who explored regulatory and health technology assessment considerations and emerging "good practices" for the development and use of AI in healthcare and therapeutic development. This publication, which is based on the work of the WG-RC, is an Overview of Regulatory Considerations on Artificial Intelligence for Health that covers the following six general topic areas: Documentation & Transparency, Total Product Lifecycle Approach & Risk Management, Intended Use and Analytical

& Clinical Validation, Privacy and Data Protection, and Engagement & Collaboration. This overview is not intended as a guidance, regulation, or policy. Rather, it is meant as a listing of key regulatory concepts and a resource that can be considered by all relevant stakeholders in medical devices ecosystems, including but not limited to, developers who are exploring and developing AI solutions, regulators who might be in the process of identifying approaches to manage and facilitate AI solutions, manufacturers who design and develop AI-embedded medical devices, health practitioners who deploy and use such medical devices and AI solutions, and those working to remit. The WG-RC recommends that stakeholders examine these key considerations and other potential considerations as they continue to develop frameworks and best practices for the use of AI in healthcare and therapeutic development in relationship to the 6 topic areas.

The WG-RC recognizes that AI has been instrumental in rapidly advancing research in healthcare and therapeutic development. However, it also recognizes the evolving complexity of the AI landscape and the need for international collaboration to facilitate the safe and appropriate development and use of AI solutions. Accordingly, international collaboration on AI regulations and standards is important for three reasons. First, sharing knowledge and best practices of evolving regulatory considerations could increase the speed of developing this regulatory landscape and reduce the gap between advancing technology and regulation. Second, international collaboration improves consistency in regulations, which is important as many tools will likely eventually cross borders. Regulatory consistency could improve standards and enable more rapid deployment. Finally, international collaboration supports countries with less regulatory capacity by ensuring that these countries can also use tools with high standards, reducing the potential for disparity in the introduction of these tools.

**Commented [MR132]:** Regulatory consistency is I think conceptually distinct from harmonisation, which can be more problematic. Would be good to be clear here.

The WG-RC understands that the AI landscape is rapidly evolving and that the considerations in this deliverable may need to be expanded upon as the technology and its uses develop. It recommends that stakeholders, including regulators and developers, continue to engage and that the community at large works towards shared understanding and mutual learning. In addition, established national and international groups, such as the IMDRF and ICH, should consider the topic of AI for potential standardization (where useful) and for harmonization efforts in general.

# Annex A: List of Acronyms, Definitions, and Fundamental Concepts

For the purpose of this document, the following definitions and overarching concepts applies:

- ## Acronyms

| | |
|---|---|
| **WHO** | World Health Organization |
| **AI** | Artificial Intelligence |
| **ITU** | International Telecommunication Union |
| **FG-AI4H** | Focus Group on Artificial Intelligence for Health |
| **WG-RC** | Working Group on Regulatory Considerations on Artificial Intelligence for Health |
| **IMDRF** | International Medical Device Regulators Forum |
| **ICH** | International Council for Harmonization of Technical Requirements for Pharmaceutical for Human Use |
| **NLP** | Natural Language Processing |
| **OECD** | The Organisation for Economic Co-operation and Development |
| **CONSORT-AI** | Consolidated Standards of Reporting Trials for AI |
| **SPIRIT-AI** | Standard Protocol Items: Recommendations for Interventional Trials for AI |
| **SaMD** | Software as a Medical Device |
| **FDA** | Food and Drug Administration |
| **ML** | Machine Learning |
| **TPLC** | Total Product Lifecycle |
| **PACMP** | Post-Approval Change Management Protocol |
| **NICE** | National Institute for Health and Care Excellence |
| **PDPC** | Singapore Personal Data Protection Act |
| **IoT** | Internet of Things |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **GDPR** | General Data Protection Regulation |
| **EU** | European Union |
| **UNCTAD** | United Nations Conference on Trade and Development |
| **NIST** | National Institute of Standards and Technology |
| **SAHPRA** | South African Health Products Regulatory Authority |
| **MHRA** | Products Regulatory Agency |
| **EC** | European Commission |
| **HSA** | Health Sciences Authority |
| **SANAS** | South African National Accreditation System |
| **QMS** | Quality Management System |
| **TGA** | Therapeutic Goods Administration |
| **NHS** | National Health Service |
| **CQC** | Care Quality Commission |
| **PRISM** | Pharmaceutical Regulatory Information System |

| | |
|---|---|
| **CRM-N** | Clinical Research Materials Notification |
| **SARs** | Special Access Routes |
| **CDSS** | Clinical Decision Support System |
| **MAS** | Multi-Agent Systems |

- **Definitions and Concepts**

### 1. Artificial Intelligence

AI is the science of creating machines capable of performing tasks that normally require human intelligence[125].

### 2. Trustworthiness

The Organizsation for Economic Co-operation and Development (OECD) recommendation for AI solutions identifies complementary values-based principles for the responsible stewardship of trustworthy AI[126] across all sectors including healthcare. AI solutions' stakeholders involved in their development, deployment, or operation should be held accountable for their proper functioning in line with the following principles:

- AI should benefit people and the planet by driving inclusive growth, sustainable development and well-being.
- AI solutions should be designed in a way that respects the rule of law, human rights, democratic values and diversity, and they should include appropriate safeguards– for example, enabling human intervention where necessary– to ensure a fair and just society.
- There should be transparency and responsible disclosure around AI solutions to ensure that people understand AI-based outcomes and can challenge them.
- AI solutions must function in a robust, secure, and safe way throughout their life cycles and potential risks should be continually assessed and managed.

### 3. Transparency

The term transparency, in the context of this publication, refers to issues such as sharing and making available to the appropriate entities, the relevant plans, decisions, and associated reasoning and the data/datasets utilized in the conception, development and ongoing deployment and monitoring of AI solutions. Transparency is multifaceted and may include public dissemination by publications in peer-reviewed journals, publishing and documenting pre-specifications for development processes including clinical trials, etc.

### 4. Documentation

For the purpose of this document, the term documentation refers to processes and methods used to document, retain, and prespecify critical development ideas, including the initial conception, validation and deployment, and post-deployment plans, as well as relevant key decisions and choices and supporting rationale (e.g., selection of data/datasets) used in the development of AI solutions for health and therapeutic development throughout the total life cycle (e.g., from conception to post-deployment). Methods and approaches for risk and error management, reporting, and detection of bias are all key areas for documentation. Documentation can also help facilitate the understanding of algorithm decision-making process (explainability). Documentation should allow for the tracing and audits of the development process and the steps taken in the development and

[125] https://www.statnews.com/wp-content/uploads/2021/04/Promise_and_Peril_STAT_Report_2021.pdf

[126] The Organisation for Economic Co-operation and Development (OECD) Principles on AI. OECD; (2019) (https://www.oecd.org/going-digital/ai/principles/).

**Commented [PR133]:** Consider adding a qualifier here: This section applies to definitions and concepts as they are used for the purpose of this document.

If the qualifier is added here, it can be deleted under the individual definitions.

**Commented [dr134]:** 1-4 in trustworthiness are the principles. These are important and should be its own para of the principles, and not definition

**Commented [M(135]:** This is not properly a definition - it is more a discussion of what it should be, how to obtain it. A definition would be for me something like: "Trustworthy AI in the context of this document refers to AI technology that meet stakeholders expectation in terms of bias, explainability, provenance and other desirable characteristics." (to be refined.) Then this text with the OECD criteria could go eg as a new Section 4 on itself.
BUT - read my commnet above for the whole section.

**Commented [aa136]:** To much details beyond the the definition unless this is a different section. Also, you mentioned 5 values-based while you talked only 4

**Commented [M(137]:** This like above goes beyond definition. Maybe move down.

validation of the AI solution if needed and appropriate. This includes ensuring that changes and deviations from prespecified approaches and protocols are tracked, recorded, and justified. Although effective documentation is only one element that supports transparency, it is a key regulatory principle.

Commented [M(138]: This like above goes beyond definition. Maybe move down.

### 5. Privacy

Privacy is a broad and multidimensional concept. It is a universally accepted fundamental human right[127] ~~and~~. ~~in~~ In nearly every nation, numerous statutes, constitutional rights, and judicial decisions seek to protect privacy. The concept of privacy includes the control over personal information, often referred to as data or information privacy. Data privacy is focused on the use and governance of personal data, including implementing policies to ensure that consumers' personal information is being collected, shared, and used in appropriate ways[128]. Privacy risks include reidentification, as well as the release of unwanted inferences about a data subject (e.g., whether they have a certain disease)[129].

### 6. Data protection

Data protection is a more technical issue under the broader umbrella of privacy. It includes the requirements and methods used to store and organize data in a physically secured manner to prevent unauthorized access and use. Data protection is focused on securing data against malicious attacks and preventing the potential exploitation of stolen data for profit. While security is necessary for protecting data, it may not be sufficient for addressing privacy[130].

Commented ['W139]: Privacy: Privacy includes not only the protection of a person's personal data. There are more privacy domains. Electronic communications and letters (letter secret) should be treated confidential and not intercepted, conversations should not be eavesdropped, intercepted, or recorded. A person should not be simply be strip-searched, or fingerprinted. Body fluids may not simply be taken, including DNA samples. A person's home residence should not be simply searched. Surely there are more examples of actions by third parties which affect the privacy.

Data protection:
This is also a legal issue.

Commented [PR140R139]: This does not exclude other definitions of privacy. The focus is on data protection, not the multifaceted domains of the right to privacy.

### 7. Health data

Health data is personal data relating to the physical or mental health of a person, and includes the provision of healthcare services, and information regarding a person's health status[131]. Health data is often considered a special category of personal data, or 'sensitive' personal data, because of the nature and influence such data has on human lives and its impact on their fundamental rights and freedoms.

### 8. Sources of health data

Sources of health data include data acquired from digital health and medical technologies, such as wearable devices, digital health (or electronic health) applications, and medical devices and sensors; electronic health records and administrative hospital data; data from aggregated clinical trials; bioimaging and genomic data from the sequencing of human biological materials; health-related geospatial and contact tracing data; insurance claims; and data from social media, smart phones, ~~wearables~~, and other electronic devices. The health data, or special personal data, derived from these sources, including heart rate, blood glucose, genetic predispositions, fitness levels, age, weight and so on, may be subject to data protection and privacy laws. Although these laws may vary from country to country as later discussed in this section, they will inform how the data is processed and for what purpose.

Commented [pa141]: Consider adding "wearables" to this sentence

Commented [RP142R141]: Wearables is the first example listed

Commented [MR143]: A helpful diagram of the sources of health data can be found here: https://www.who.int/ehealth/resources/ecosystem.pdf?ua=1

Commented [aa144]: how about the bias and ethical considerations

[127] According to the United Nations Universal Declaration of Human Rights of 1948, "No one shall be subjected to arbitrary interference with his privacy, family, home or correspondence, nor to attacks upon his honor and reputation."
[128] What is Privacy? IAPP. (2020) (https://iapp.org/about/what-is-privacy/)
[129] Kearns, Michael, and Aaron Roth. *The Ethical Algorithm: The Science of Socially Aware Algorithm Design*. Oxford University Press, 2020, 33.
[130] What is Privacy? IAPP. (2020) (https://iapp.org/about/what-is-privacy/)
[131] EU General Data Protection Regulation 2016/679.