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**Overview of Regulatory Considerations on Artificial Intelligence for Health**

Working Group on Regulatory Considerations

on Artificial Intelligence for Health

*Draft v2.1*

*19/03/2021*

# Acknowledgements

To be updated.

# 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

To be updated.

# 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 |
| **NLP** | Natural Language Processing |
| **OECD** | The Organisation for Economic Co-operation and Development |
| **CONSORT** | Consolidated Standards of Reporting Trials |
| **SPIRIT** | Standard Protocol Items: Recommendations for Interventional Trials |
| **ML** | Machine Learning |
| **FDA** | Food and Drug Administration |
| **SaMD** | Software as a Medical Device |
| **IMDRF** | International Medical Device Regulators Forum |
| **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 |

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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[[1]](#footnote-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[[2]](#footnote-3) and the triple billion targets of WHO’s Thirteenth General Programme of Work, 2019–2023[[3]](#footnote-4).

Although digital transformation of healthcare can be troublesome, technologies including Artificial Intelligence (AI) have proven potential to enhance health outcomes by improving medical diagnosis, data-based treatment decisions, 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 AI phenomenon of machines being able to solve problems that once was believed would require human intelligence has recently seen an enormous rise of interest due to the recognition of its great potential. 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.

1. **Purpose**

In order to facilitate the safe and appropriate development and use of AI solutions[[4]](#footnote-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 aimed as a general, high-level, and nonexclusive overview of key regulatory considerations’ topic areas delivered by the WG-RC on AI for health, which supports 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, the WG-RC will take into consideration different stakeholder perspectives, as well as different global and regional settings. This WG-RC’s 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.

# Basic Concepts

For the purpose of this document, a number of fundamental overarching concepts are defined below:

* **Artificial Intelligence**

Artificial intelligence is the science of creating machines capable of performing tasks that normally require human intelligence[[5]](#footnote-6).

* **Trustworthiness**

The Organisation for Economic Co-operation and Development (OECD) recommendation for AI solutions identifies five complementary values-based principles for the responsible stewardship of trustworthy AI[[6]](#footnote-7) 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:

1. AI should benefit people and the planet by driving inclusive growth, sustainable development and well-being.
2. 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.
3. There should be transparency and responsible disclosure around AI solutions to ensure that people understand AI-based outcomes and can challenge them.
4. AI solutions must function in a robust, secure and safe way throughout their life cycles and potential risks should be continually assessed and managed.

* **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.

* **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 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.

* **Privacy**

Privacy is a broad and multidimensional concept.It is a universally accepted fundamental human right[[7]](#footnote-8) and 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[[8]](#footnote-9). Privacy risks include reidentification, as well as the release of unwanted inferences about a data subject (e.g., whether they have a certain disease)[[9]](#footnote-10).

* **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[[10]](#footnote-11).

* **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[[11]](#footnote-12). 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.

* **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.

# AI Applications in Healthcare

Rapid prototype technologies have been developed with increasing 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[[12]](#footnote-13). Many health-related technical 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, as illustrated in Figure 1 below.

Prevention & Health promotion

Screening

Diagnosis

Treatment

Surveillance

End of Life Care

Research and Development

Resource Allocation & Healthcare Management

Figure 1 The spectrum of research and development in healthcare delivery and therapeutic development.

AI solutions in healthcare could support patients throughout the phases of a disease, such as supporting adherence to therapeutics and enhancing communication capabilities with care providers. Furthermore, healthcare is striving to become more patient-centric by using a personalised, evidence-based approach to decision-making[[13]](#footnote-14). This allows data to be used to improve patient and population wellness, patient education and engagement, prediction of diseases and care risks, medication adherence, disease management, disease reversal/remission, and individualization and personalization of treatment and care. Moreover, AI solutions have been introduced to aid in early drug discovery of candidate therapies, modelling, and prediction. Finally, AI also supports downstream drug development, including associated medical devices (e.g. Software as Medical Device (SaMD)) and drug development (e.g. combination therapy design); diagnostic tests; as well as clinical decision making, such as AI solutions that facilitate clinical studies and clinical evaluations; support diagnostics and disease staging efforts; and determine appropriate therapeutics and course of therapy. Hence, the majority of AI applications can be categorized in a framework and they may fall into one or more of the following categories[[14]](#footnote-15): prevention, prediction, diagnosis, behavior modification, follow-up care, personalized treatment, and drug discovery as illustrated in Figure 2 below.



Figure 2 Framework of AI applications in healthcare delivery and therapeutic development.

The abovecategorisation 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.

# 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 developers and regulators is highly advised as the community at large is continuing to establish a common understanding around the use of the AI solutions in health. .

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 discussed below. The working group divided into subgroups composed of subject matter experts to draft a section oon each topic area. The WG-RC would like to highlight that this 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.

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 |

* + **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 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.

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 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. 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 protected against data manipulation and adversarial attacks.

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. 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 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 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 Standards of Reporting Trials for AI (CONSORT-AI)[[15]](#footnote-16), and Standard Protocol Items: Recommendations for Interventional Trials for AI (SPIRIT-AI)[[16]](#footnote-17) 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.

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.

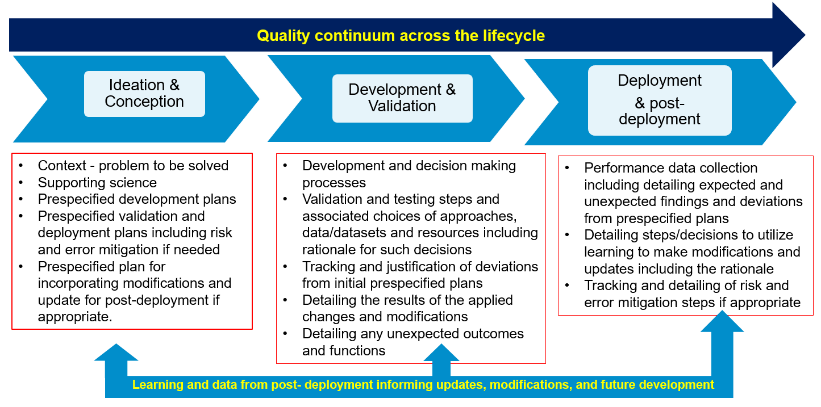


Figure 3 Examples of key development decision points in AI solutions development [[17]](#footnote-18)

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***

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.hOnce 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. Documenting how the AI solution should function in such active environments needs to be considered. As shown in Figure 3 there are multiple processes, validation steps and protocols that should be pre-specified and documented t. Pre-specification is one of the most important elements that supports trust and confidence in the development process. This will show evidence of a coherent development process and will be the basis for providing justifications and rationale for any future deviations and modifications.

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

AI solutions are designed using data and datasets from specific populations, for specific end-users, and for specific contexts. If they need to be utilized in regulated areas by 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. l 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 approach should also be considered for the level of documentation and record keeping utilized for AI solutions. Developers of AI solutions should keep in mind that regulatory organizations have avenues for dialogue 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 International Medical Device Regulators Forum (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*.”[[18]](#footnote-19) The US Food and Drug Administration (FDA) foresees the great potential of such AI-based software as a medical device in transforming healthcare due to the potential ability to learn from real-world feedback (training) and improve performance (adaptation)[[19]](#footnote-20)[[20]](#footnote-21).

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[[21]](#footnote-22). 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 life cycle 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 4 The process of developing and deployment of the AI medical device[[22]](#footnote-23)

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 13485 based quality management system[[23]](#footnote-24). Next to clinical endpoints, AI-specfic monitoring dimensions include confidence[[24]](#footnote-25), bias and robustness[[25]](#footnote-26), 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 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.



Figure 5 AI medical Total Product Lifecycle approach on AI workflow[[26]](#footnote-27).

* ***Holistic risk management***

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.



Figure 6 IMDRF schematic representation of the security risk management process[[27]](#footnote-28).

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 7 General AI medical device risk management approach.

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)

* **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[[28]](#footnote-29). 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 identifies two major factors that 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.

Table 2 AI medical devices risk classification[[29]](#footnote-30)

|  |  |  |  |
| --- | --- | --- | --- |
| 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 |

The intended use and risk classificationshould 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). Transparency among stakeholders can be achieved through proper documentation of risk management. Transparency can also be achieved through proper auditing. 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 need to be in compliance with for the development and deployment of 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 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[[30]](#footnote-31).

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[[31]](#footnote-32): 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.

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).



*Figure 8 The UK National Health Service (NHS) Buyer’s Guide to AI in Health and Care[[32]](#footnote-33)*

* ***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 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[[33]](#footnote-34). 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[[34]](#footnote-35). The PACMP is illustrated below in Figure 9.



Figure 9 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).



Figure 10 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[[35]](#footnote-36) (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. It is not intended to replace this guidance, but by outlining key considerations, to describe where challenges remain in this rapidly changing field with particular respect to low- and middle-income countries with under-resourced settings with little national regulatory or health technology evaluation capacity, and tools that may not require formal regulatory approval. 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[[36]](#footnote-37).

* ***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 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, 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 previous unencountered). Developers should also provide a clear clinical and scientific explanation of the tools’ intended performance. Standardized reporting templates common to all stakeholders can help to more effectively communicate the intended use[[37]](#footnote-38) [[38]](#footnote-39)[[39]](#footnote-40)For some intended use cases there may be clear reasons why analytical performance of the tool would differ in different settings[[40]](#footnote-41) (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[[41]](#footnote-42) (for example retinal tools have been shown to have a similar performance in different populations[[42]](#footnote-43)). Understanding of the generalizability of similar tools may be considered when providing a statement of the intended use or description of the use case[[43]](#footnote-44).

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. Developers and regulators should expect that the AI tool has been externally validated in a dataset that is independent from that in which it was trained (not merely an unseen portion of the training dataset) in order to demonstrate external validity. 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 underrepresented in the external dataset. Failure cases particularly those that are surprising or unusual should also be identified[[44]](#footnote-45).

Diagram

Description automatically generated

Figure 11 Overview of datasets involved in a machine learning diagnostic algorithm: model development and evaluation[[45]](#footnote-46)

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 limitation elsewhere in the health setting affecting access to diagnosis and treatment. These major challenges have the potential to not only propagate 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[[46]](#footnote-47)).

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. 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.

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[[47]](#footnote-48). 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. 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[[48]](#footnote-49) provides guidance on the methods, processes and software development for the analytical validation of health AIs[[49]](#footnote-50).

* ***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 condition)[[50]](#footnote-51),[[51]](#footnote-52). The IMDRF document on clinical evaluation of SaMD (illustrated earlier in Table 2[[52]](#footnote-53)) 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[[53]](#footnote-54). However currently there remains a small number of actively recruiting or completed randomised trials in this field[[54]](#footnote-55).

Randomised clinical trials have potential limitations that may make other options preferable (they are widely acknowledged to be slow, expensive, and evaluate performance in specific groups under trial conditions). Where randomised evidence is not required, prospective validation, in a real-world deployment and implementation trial, with a comparison group showing improvement in relevant outcomes using validated tools or widely accepted and verified endpoints 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.

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.

* ***Cost effectiveness***

A further component of evaluation of AI solutions in health is to consider the cost effectiveness of these tools. Investments in AI based tools must represent good value to procurers, particularly in low- and middle-income countries where the potential gains may be transformative, but where spending on digital tools may come with a high opportunity cost. The World Bank have recently published a reference case for economic evaluation of digital health interventions (NL – due in next few weeks, need to add reference when published), including those enabled by AI. This reference gives guidance to those planning, conducting and using economic evaluations of digital health tools. Those developing and proposing, or procuring AI solutions should use this framework, which includes the requirement to consider a comparator, in the evaluation of cost effectiveness of a health AI tool. Costs consider must include the ongoing costs of maintenance beyond the introduction of a tool, and be context appropriate.

The following special considerations are specific to

* ***Post market safety monitoring***

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 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***

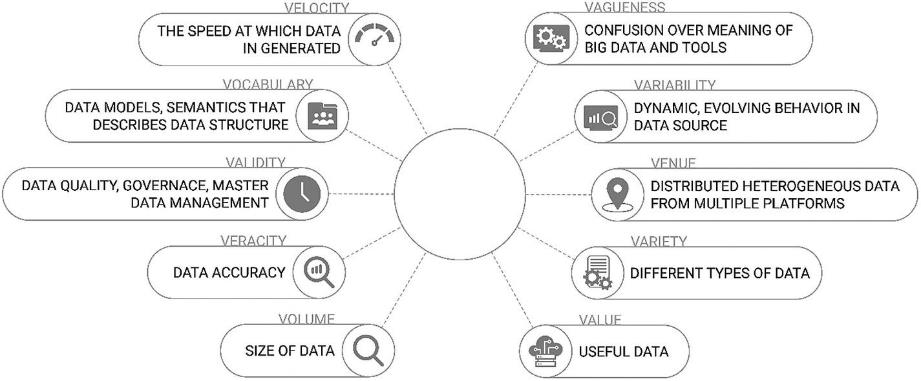
There is considerable variation in the experience of international regulatory bodies with AI tools. Some countries also lack a dedicated national regulatory body. The WG-RC meetings have provided a forum for the sharing of expertise and discussion of common problems, including regulatory bodies and other 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. However, the full context of healthcare infrastructures 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 AI benefits thanks to the explosion of data and accessibility to computation power. Data is the most important ingredient for training AI/ML algorithms in AI solutions, and it 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 the following 10Vs[[55]](#footnote-56) (as illustrated in Figure 12 below): Volume, Veracity, Validity, Vocabulary, Velocity, Vagueness, Variability, Venue, Variety, and Value.

* ***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.

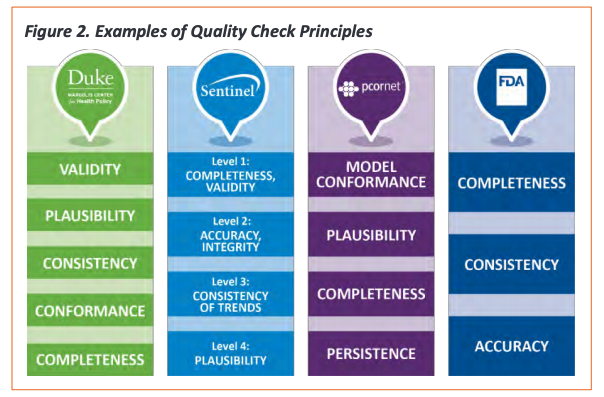


*Figure 12 The 10Vs of data[[56]](#footnote-57).*

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

The realization of AI and ML in health could not be more welcome in current health ecosystems. However, the availability of good quality datasets that are clinically relevant is one of the key challenges developers face. The lack of good quality datasets in AI solutions can 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:

* **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 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.



From: https://healthpolicy.duke.edu/sites/default/files/2019-11/rwd\_reliability.pdf

* **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[[57]](#footnote-58) that shows 71% of patient data from just three states trains most AI diagnostic tools.
* **Data labelling.** It is important toensure 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 in reporting representativeness, completeness, and other data quality characteristics have been devised by the machine learning community
* **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 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.

Below is a classified list that summarizes the key data quality considerations for AI solutions’ safety and effectiveness[[58]](#footnote-59):

*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 WHO Global Strategy on Digital Health 2020–2025[[59]](#footnote-60) 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.

* ***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 that should be considered.

Stakeholders should carefully consider the potential scientific and ethical 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. This section discusses high-level considerations for privacy and data protection. For other ethical considerations, refer to the deliverable of the Working Group on Ethical Considerations on AI for Health[[60]](#footnote-61).

Vast quantities of health-related data can be collected, stored, repurposed, modified, and linked on an increasingly unprecedent scale. This advancement in combination with new computational methods used in data analytics, especially machine learning, is transforming health research and innovation. Data-centric research and innovation can assist in developing clinically beneficial predictive models, advancing the diagnosis, treatment, and prevention of diseases, and improving the quality and efficiency of healthcare delivery systems.

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.

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[[61]](#footnote-62).

* ***Current Landscape***

Over 130 countries and regions have data protection regulations and privacy laws regulating the collection, use, disclosure, and security of personal information[[62]](#footnote-63). 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 very complex and may have conflicting obligations.

When developing an AI solution for therapeutic development or healthcare applications, early in the development process developers 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 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[[63]](#footnote-64) may apply to the personal data of European Union (EU) data subjects, regardless of jurisdiction.[[64]](#footnote-65) 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[[65]](#footnote-66). To date, the EU Commission has only recognized 13 countries as providing adequate protection[[66]](#footnote-67).

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 consider taking 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[[67]](#footnote-68). 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)[[68]](#footnote-69). 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[[69]](#footnote-70)).

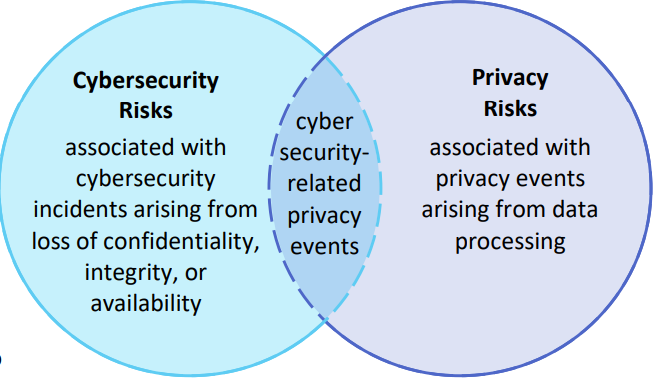


Figure 13 NIST Privacy Framework – Cybersecurity and Privacy Risk Relationship.

Figure 14 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 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[[70]](#footnote-71) and India’s proposed data privacy by design policy[[71]](#footnote-72), while others include the duty to implement and maintain reasonable security practices and procedures appropriate to the risk.[[72]](#footnote-73) 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[[73]](#footnote-74), require companies to conduct these assessments[[74]](#footnote-75). 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” [[75]](#footnote-76).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[[76]](#footnote-77). 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[[77]](#footnote-78). 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 methods of secure destruction. Developers may also consider documenting systems and approaches used to protect against data manipulation and adversarial attacks[[78]](#footnote-79).

* + **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 during thedevelopment 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 educators; and patients, patient advocates[[79]](#footnote-80) * Academia/industry[[80]](#footnote-81) * Government bodies and Congress[[81]](#footnote-82) * Foreign governments[[82]](#footnote-83) | * To respond to requests related to FDA authority[[83]](#footnote-84) * To create mutual learning opportunities and knowledge exchange for promoting and protecting public health[[84]](#footnote-85) * To acquire reviews and contributions to reports, learn about advancements, and inform the field about policies[[85]](#footnote-86) * To learn about and contribute to scientific and technical advancements [[86]](#footnote-87) * To develop and inform the field about impactful policies[[87]](#footnote-88) * To protect and promote public health[[88]](#footnote-89) * Collaborate with government agencies to expand health IT efforts, interoperability of data to establish strong connections among stakeholders for advancing scientific, technical and regulatory framework[[89]](#footnote-90) * Alignment[[90]](#footnote-91) * Mutual assessments and sharing lessons learned[[91]](#footnote-92) * Harmonizing best practices and guidance documents[[92]](#footnote-93) | * Patient outreach Newsroom and MedWatch[[93]](#footnote-94) * Public and private partnerships[[94]](#footnote-95) * Training modules and education programs[[95]](#footnote-96) * Collaborative research projects through partnerships and research collaboration agreements [[96]](#footnote-97) * Enabling networking among experts (e.g., regulatory associations, patient advocacy groups) * Workshops[[97]](#footnote-98) * Diversification of staff[[98]](#footnote-99) * Digital and print media and graphics[[99]](#footnote-100) |

Table 5 Engagement and collaboration strategy of SAHPRA

|  |  |  |  |
| --- | --- | --- | --- |
| **Organization (Country)** | **With whom?** | **Why?** | **How?** |
| SAHPRA (South Africa) | * Industry (Manufacturers/ Distributors) * Academia * National department of Health * National department of Trade & Industry * Patients * Clinicians * Health technology assessments groups * Trade associations * Conformity assessment bodies * South African National Accreditation Service | * Facilitate the approval of innovative AI solutions * 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 formalised * Recommended that stakeholder engagement adopt the five-step engagement model developed by the Therapeutic Goods Administration (TGA) Australia[[100]](#footnote-101) |

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)[[101]](#footnote-102) | * Healthcare professionals and providers in the National Health Service (NHS) and in private healthcare providers * Media * Patients, patient advocates; academia; medical device and in vitro diagnostic industry; health tech industry sector; consumers/general public * 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) | * Alert users to problems with medical devices and medicines * Answer enquiries about role in regulation or raise awareness of safety issues * Seek feedback on development of regulatory policy, managing adverse incidents and risks * Interface with UK government and NHS including stakeholders aligned to digital and AI-related activities | * Central alerting system to the NHS and healthcare providers or through professional groups * Media, public, and other stakeholder inquiries via MHRA Customer Service Centre, dedicated email inboxes, and Press Office * Connecting with Expert Advisory Groups, networks, and stakeholder groups on specific issues * Consultation on engagement with patients and public[[102]](#footnote-103) * 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)[[103]](#footnote-104) | * “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[[104]](#footnote-105) 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 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)[[105]](#footnote-106),[[106]](#footnote-107) | * 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 * Manufacturers, software and AI developers. Industry and Trade Associations * Other government agencies responsible for deployment of technologies in healthcare system, healthcare professionals, and professional groups, healthcare institutions, | * Early engagement and support to innovators to facilitate regulatory compliance thus facilitating timely access to safe innovations for patients * 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 Cycle Approach[[107]](#footnote-108) * 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 | * Rapid, streamlined engagement portals are available for several facets of product regulation[[108]](#footnote-109) * Specific processes that can be straightforwardly addressed include Medical Device Information Communication System (for application submissions for licenses, permits, registrations, etc.) * 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]](https://euc-word-edit.officeapps.live.com/we/wordeditorframe.aspx?ui=en-us&rs=en-us&wopisrc=https%3A%2F%2Fworldhealthorg.sharepoint.com%2Fsites%2FAI4HWGRC%2F_vti_bin%2Fwopi.ashx%2Ffiles%2F906e1d4253d14ebd88b6f1058a0586ce&wdenableroaming=1&mscc=1&hid=-341&uiembed=1&uih=teams&hhdr=1&dchat=1&sc=%7B%22pmo%22%3A%22https%3A%2F%2Fteams.microsoft.com%22%2C%22pmshare%22%3Atrue%2C%22surl%22%3A%22%22%2C%22curl%22%3A%22%22%2C%22vurl%22%3A%22%22%2C%22eurl%22%3A%22https%3A%2F%2Fteams.microsoft.com%2Ffiles%2Fapps%2Fcom.microsoft.teams.files%2Ffiles%2F965658113%2Fopen%3Fagent%3Dpostmessage%26objectUrl%3Dhttps%253A%252F%252Fworldhealthorg.sharepoint.com%252Fsites%252FAI4HWGRC%252FShared%2520Documents%252FGeneral%252FWG-RC%2520DEL02%2520Versions%252FWG-RC_DEL02-v2-With-Tracked-Changes.docx%26fileId%3D906e1d42-53d1-4ebd-88b6-f1058a0586ce%26fileType%3Ddocx%26ctx%3Daggregate%26scenarioId%3D341%26locale%3Den-us%26theme%3Ddefault%26version%3D21021008600%26setting%3Dring.id%3Ageneral%26setting%3DcreatedTime%3A1618040598657%22%7D&wdorigin=TEAMS-ELECTRON.aggregatefiles.aggregate&wdhostclicktime=1618040598334&jsapi=1&jsapiver=v1&newsession=1&corrid=ad11001e-6e86-4468-b462-baacfb513824&usid=ad11001e-6e86-4468-b462-baacfb513824&sftc=1&sams=1&accloop=1&sdr=6&scnd=1&hbcv=1&htv=1&hodflp=1&instantedit=1&wopicomplete=1&wdredirectionreason=Unified_SingleFlush&rct=Medium&ctp=LeastProtected#_ftn1) * **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 * Online stakeholder consultation process for all new and revised policies and guidelines * Regular focus group discussions and engagements with industry associations and companies |

* ***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 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. [[109]](#footnote-110)￼[[110]](#footnote-111)[[111]](#footnote-112)

* ***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 and/or combinations recommended by these platforms[[112]](#footnote-113),[[113]](#footnote-114),[[114]](#footnote-115). 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[[115]](#footnote-116) 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 personalised 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.[[116]](#footnote-117),[[117]](#footnote-118),[[118]](#footnote-119) 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 personalised based on (e.g.,) the individualised 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.[[119]](#footnote-120)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 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 optimised 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 programme because it stipulates a prerequisite of an initial assessment of device risk from the HSA.[[120]](#footnote-121) 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.[[121]](#footnote-122) 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 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.[[122]](#footnote-123)

* ***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 programme. 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[[123]](#footnote-124) 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[[124]](#footnote-125). 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 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, enablesworking alongsidethe 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 mindset approach to regulation of AI products and services one step further, co-regulation, could be explored. As outlined by Clark[[125]](#footnote-126), 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[[126]](#footnote-127). 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.

# Recommendations for the Way Forward

1. The Working Group on Regulatory Consideration has provided a forum for regulators and allied experts to discuss the current regulatory landscape and describe current best practice. Recognizing the desire of many agencies to create a robust and astreamlined regulatory environment to facilitate the evaluation and adoption of safe and effective AI tools, the Working Group has delineated a set of recommendations that should be considered by agencies as they move to update their current regulatory procedures:
3. Tools developed with AI technology are heavily reliant on the underlying training datasets. Composition of these training datasets should reflect the populations where these tools will eventually be used, and should follow external validation processes. Transparency of data, used in training and validation, are therefore critical to ensure that tools are not used beyond the environments in which they have been shown to be safe and effective. Examples of how to transparently present this information have been described in a proposed framework bySendak et al (<https://www.nature.com/articles/s41746-020-0253-3>). This framework proposes that in addition to key information (description of the model type, the target population and the input and output data type), performance of the model in different validation settings and steps should be reported, and long with warnings about clinical situations or settings where the model has not been validated.
4. The Working Group would also recommended that information about the size and the demographics compositions of the training datasets and validation cohorts are reported.
5. Concerns currently exist about the potential for bias in AI tools, which may arise for many reasons including unequal and non-representative training or validation data or due to structural bias in the healthcare system in which the model was trained. Introducing a requirement to report the gender, race and ethnicity characteristics of the people included in the training and validation data cohorts would enable transparency about potential for bias stemming from data representativeness. Warnings may be required for populations for which the tool has not been validated, and post marketing surveillance should enable close monitoring for the potential of bias.
6. Current processes for regulation, thatcenter around a single approval step, may require an alternative approach for AI tools. Given the novelty of the approach, the lack of high-quality evidence in many areas, and the emerging consensus around the importance of prospective, real world surveillance for adequate evaluation of model performance, a period of mandatory post deployment surveillance could be considered as a mandatory requirement for full approval of high-risk tools.
7. While most regulatory agencies have national or regional remits, there is currently a reliance within some countries with lower regulatory capacity on the decision made by other major regulators. The performance of AI tools is highly dependent on the context, and therefore providing maximum transparency of the data submitted for regulatory approval and facilitating a local ‘second step’ validation for tools that have received regulatory approval with local or regional agencies could optimize this process.
8. In order for regional, national or local agencies to effectively carry out a ‘second step’ local validation, there is a need for high quality data, representative of the clinical context and population in which it is intended to be used. For could require an investment of resources to create datasets for validation. 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 creation of datasets to support validation.
9. Many local and national agencies are interested in the ability to benchmark AI tools. As described above, this will require locally representative data, and benchmarking such AI tools could facilitate a number of key functions: a local validation step to ensure the performance of the tool in the local population, an ability to check the performance of AI tools that are either continuously learning or have been updated, and the ability to understand the comparative performance of tools. The Open Code Initiative, part of the WHO/ITU focus group are developing a platform for benchmarking of AI tools, which could be used in this way.
10. Recognizing that regulatory authorities largely have national or regional remits, the Working Group coordinated by the WHO and ITU has enabled regulatory agencies to discuss current challenges, share their best practices, and create a series of recommendations for consideration as agencies continue to work on their approach to AI tools.
11. Thefield of AI regulation continues to evolve rapidly, and the Working Group recommends that the WHO/ITU continue to facilitate this exchange. Recognizing that other groups already exist in this area, and provide important forums for exchange and valuable guidance to the industry, there are numerous countries that do not have strong regulatory capacity yet, and are not able to participate in these mechanisms. Considering regulatory aspects of AI, through the specific lens of the SDGs has provided a number of important and additional recommendations.

# Conclusion

AI has been instrumental in rapidly advancing research in the healthcare. AI for medical devices is subject to all applicable state, local, federal and national laws and regulations. At present, in many areas, the pace of change in available technology has moved faster than the corresponding standards and regulations. Many national agencies are working on this, and has been discussed in international groups such as IMDRF and GDHP recent whitepaper. International collaboration on AI regulations and standards is important for three reasons. First, sharing knowledge and best practice of evolving regulatory considerations increases the speed of developing this regulatory landscape and reduces the gap between technology and regulation. Second, international collaboration and cooperation improves consistency in regulations which is important as many tools will likely eventually cross borders, some consistency in regulation improves standards and enable rapid deployment. Finally, it supports countries with less regulatory capacity ensuring that countries with less capacity can also use tools with high standards and reduces the potential for disparity in the introduction of these tools.

The WG-RC is open to all, and has acted as a key discussion group not only among regulators, but also academics, clinicians, developers and those responsible for health technology assessment and procurement. Through these discussions the group were able to set out current considerations and current best practice, but also have developed a number of recommendations that could be considered by regulators, and other stakeholders in the area to progress the development of an international community of standards.

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