NUS Initiative to Improve Health in Asia

Artificial Intelligence in Healthcare: Landscape, Policies and Regulations in Asia-Pacific

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Duke-NUS Medical School

NUS National University of Singapore | NUS Global Asia Institute

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Preface

The National University of Singapore (NUS) Initiative to Improve Health in Asia (NIHA) was established in 2010 with funding support from the Singapore Economic Development Board (EDB) and GlaxoSmithKline. This initiative aims to progress and strengthen public health and healthcare delivery in the Asia-Pacific region through improved research, governance, and sustainable financing. As such, NIHA developed three integrated programmes to achieve this:

- **Leadership programme.** To equip healthcare leaders across the region with important leadership competencies to tackle relevant healthcare issues, and drive health and healthcare innovation in the region.
- **Research.** To develop innovative solutions to the pressing healthcare challenges facing the region and to promote evidence-based health policy.
- **Policy forums.** To foster dialogue and partnerships among policy makers, non-governmental organisations, academia, and the private sector on the opportunities and challenges of healthcare in the region.

As the world undergoes a digital revolution, technological advancements are transforming people's way of life, including how they experience and interact with the healthcare system. While there is a need for healthcare systems and regulatory bodies to address and adapt to changing times, it is important to understand the current landscape first. Hence, NIHA held two policy forums in 2018 and 2019, on the topics of Digital Health and Artificial Intelligence in Healthcare, respectively.

The forum on Digital Health brought together key thought leaders from the medical technology (medtech) industry and various government agencies to discuss the current digital healthcare landscape and issues in the Asia-Pacific. Similarly, the forum on AI in Healthcare provided an overview of the potential impact of this topic across Asia-Pacific, including discussion on AI's regulatory challenges, and the strategies available to ensure proper conduct in this emerging field. Taking reference from the presentations that took place at these forums, this paper will provide a "tour of the horizon" of AI technology, its potential applications, and emerging regulatory considerations.

Executive Summary

As AI technology steadily advances and is more widely used in healthcare, regulators, healthcare professionals, and patients must be aware of and prepare for the resulting potential changes to the healthcare landscape and practice. While such technologies hold much promise of improving healthcare and offer novel solutions to existing and anticipated challenges, they also raise questions of safety, effectiveness, ethics, and governance that have yet to be fully explored and resolved.

This paper recognises that National Regulatory Authorities (NRAs) are a key element in the healthcare technology 'ecosystem', and thus seeks to inform regulators about the latest technological and regulatory developments of AI. It also aims to inform AI developers of the regulatory concerns they should be cognisant of while designing their products.

Based on presentations from the 2019 NIHA AI in Healthcare forum, the paper examines AI in healthcare in the Asia-Pacific context by highlighting key healthcare trends and challenges in the region. It identifies recent developments and AI applications in the industry, and spotlights potential pitfalls and risks that developers and regulators need to overcome before AI can be assuredly implemented into healthcare systems. This paper also analyses the regulatory activities of some Asia-Pacific countries and elsewhere to highlight how they have addressed various challenges and considerations when developing their national regulatory frameworks to address AI.

The paper concludes by highlighting areas and gaps for further consideration and collaborative work by policy makers, regulators, and AI developers, both locally and internationally. These include:

1. **Greater need for AI-specific guidelines,** building upon the base of existing national regulations, regional directives, international standards, and international regulatory harmonisation guidance (e.g. International Medical Device Regulatory Forum (IMDRF), Global Harmonisation Task Force (GHTF), Asian Harmonisation Working Party (AHWP), and Association of Southeast Asian Nations (ASEAN)).
2. **Application of Good Regulatory Practices** (e.g. Organisation for Economic Co-operation and Development (OECD) and ASEAN) in developing and implementing AI-specific regulations and guidance in national regulatory systems.
3. **Development of regulatory capacity** through technical training and collaboration with academic, industry, and healthcare experts; joint reviews of marketing authorisation applications by experts from more than one national regulatory authority, and use of 'regulatory reliance'.

4. **Strengthening of post-marketing monitoring systems to focus on AI-based technologies** through real world evidence over the product life cycle, especially for adaptive dynamic systems incorporating machine learning.
5. **Acknowledgement that regulatory requirements other than those specific to medical devices may also apply to AI-based healthcare technologies**, e.g. personal data privacy and telecommunications, and design accordingly.
6. **Open communication among regulators and AI developers in collaboration with standard development bodies** (e.g. International Organisation for Standardisation (ISO) and International Electrotechnical Commission (IEC)) to timely develop useful and applicable international standards for the safety and performance of AI-based healthcare technologies.
7. **Involvement of patient groups and healthcare providers** during development of AI products and regulations, to foster shared understanding on the benefits, risks, and limitations of AI, while garnering their opinion, concerns, and priorities.
8. **Promotion of coordination amongst national regulatory authorities in the Asia-Pacific regulation of AI-based healthcare technologies** to promote capacity building and leveraging of limited resources.

As AI's potential is realised over time, it is important to remember that AI has its limitations and is no substitute for human judgment and empathy, and cannot replace the human touch. As a tool intended to support and supplement people, AI's development requires healthcare professionals, regulators, and AI developers to continuously collaborate and preserve the fine balance of innovation, patient safety, and effectiveness.

Contents

List of Abbreviations

AAMI	Association for Advancement of Medical Instrumentation
AHWP	Asian Harmonisation Working Party
AI	Artificial Intelligence
AI-MD	AI Medical Device
ASEAN	Association of Southeast Asian Nations
DL	Deep Learning
EU	European Union
FDA	Food and Drug Administration
GHTF	Global Harmonisation Task Force
HSA	Health Sciences Authority
IEC	International Electrotechnical Commission
IMDRF	International Medical Device Regulatory Forum
IoT	Internet of Things
ISO	International Organisation for Standardisation
MFDS	Ministry of Food and Drug Safety
ML	Machine Learning
MOH	Ministry of Health
NIHA	National University of Singapore Initiative to Improve Health in Asia
NMPA	National Medical Product Administration
NRA	National Regulatory Authority
OECD	Organisation for Economic Co-operation and Development
SaMD	Software as a Medical Device
TGA	Therapeutic Goods Administration
US	United States

1. Introduction

The Asia-Pacific region has been experiencing many healthcare challenges in the past decade, namely a rapidly ageing population and the growing prevalence of chronic diseases as people's lifestyles become more sedentary. Such developments have increased healthcare needs and costs throughout the region, and necessitates healthcare systems to rethink their approach in managing population health. This, in conjunction with the explosion of technological advancements and the generation of massive amounts of health data, has positioned Artificial Intelligence (AI) as the potential key to new solutions and possibilities.

With its ability to "discern and learn" from such data, automate labour-intensive activities, and perform feats that humans are incapable of, AI offers a wide spectrum of applications, creating opportunities to not only improve existing healthcare delivery, but to also equip and advance healthcare systems to face future demands. However, it is important to note that AI technology is still in its infancy, and requires concerted effort from AI developers, researchers, healthcare professionals, and regulatory bodies to prepare for large-scale adoption and ensure it is ready for real-world application. Thus, regulatory agencies need to stay abreast of AI developments in healthcare to understand the risks, challenges, and capabilities, to develop regulations and policies and safeguard the well-being of people.

In this paper, based on the NIHA forums on digital health and AI in healthcare, we outline the many roles AI can play in healthcare, demonstrate their potential as seen by recent AI-based product developments, identify risks and challenges arising from AI's autonomous and adaptable nature, summarise areas for consideration when drawing up regulatory documents, spotlight regional and international regulations, policies, and discussions, and conclude with the discussions that need to take place to address the social and legal implications of AI in healthcare.

2. Background

2.1 What is Artificial Intelligence?

AI is a term that encompasses a wide range of technologies that generally have the ability to perform complex tasks commonly associated with intelligent beings, such as learning, reasoning, communicating, and making human-like decisions, and utilises different learning methods and algorithms to perform its functions.

From a programming perspective, AI can be subcategorised into machine learning (ML) and deep learning (DL) methods (Figure 1) (1).

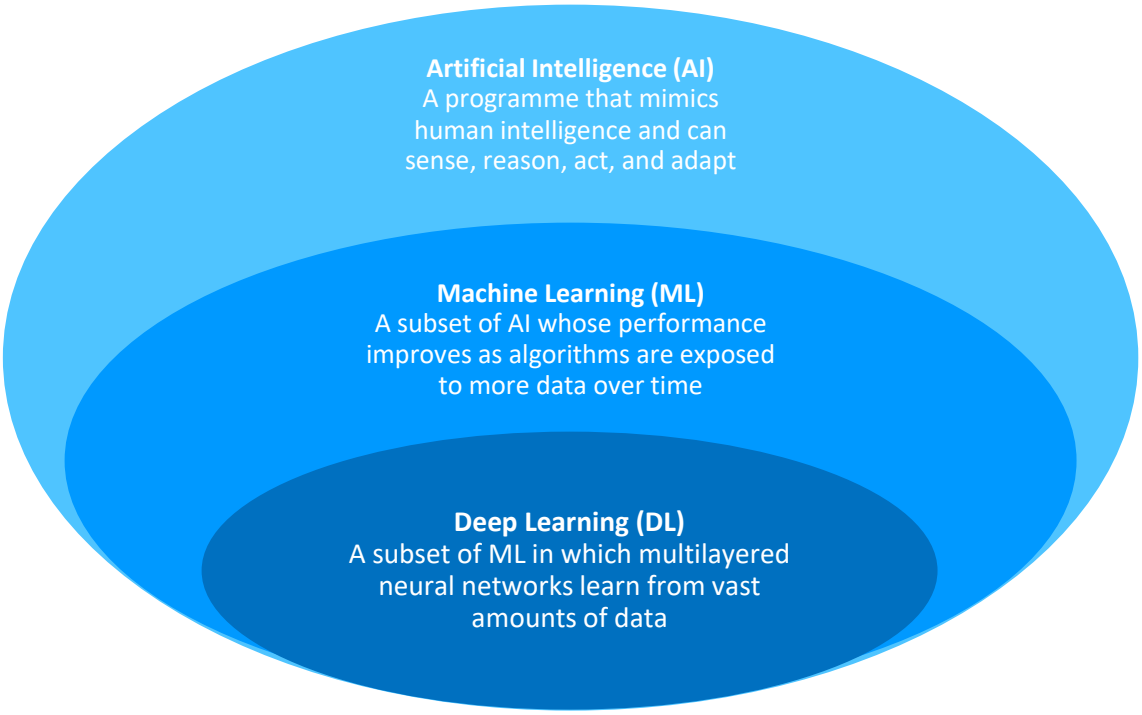

Figure 1. Classification of AI technology (1)

ML is a subset of AI involved with the creation of algorithms which can learn three ways: supervised learning, unsupervised learning, and reinforcement learning. In supervised learning systems, the algorithm learns from a training dataset mapped to labelled data. For example, if the algorithm is taught that a set of images are labelled as “cat”, the algorithm produces inferences to predict whether a new image is of a cat or not (2). In unsupervised learning systems, the algorithm discovers patterns without any labelled data. The system does not predict what the right output should be, but rather groups data points based on similarity. In reinforcement learning, also known as reward-based self-learning, the algorithm learns from trial and error, as it is rewarded or penalised depending on whether it produces the correct or incorrect output (2).

Evidently, there are multiple types of ML algorithms, ranging from classification and regression generated from supervised learning, clustering and dimension reduction from unsupervised learning, to reward-based self-learning. Each one is better suited for different types of problems, in the same way that certain statistical methods are more appropriate for certain types of analyses.

DL, as a subset of ML, uses several layers of algorithms, each providing a different interpretation of the data it feeds on. Such a network of algorithms is called artificial neural networks, as an attempt at imitating the function of the human neural networks present in the brain.

Depending on its implementation, AI can also be divided into two categories: rules-based versus data-driven. (Figure 2) (3).

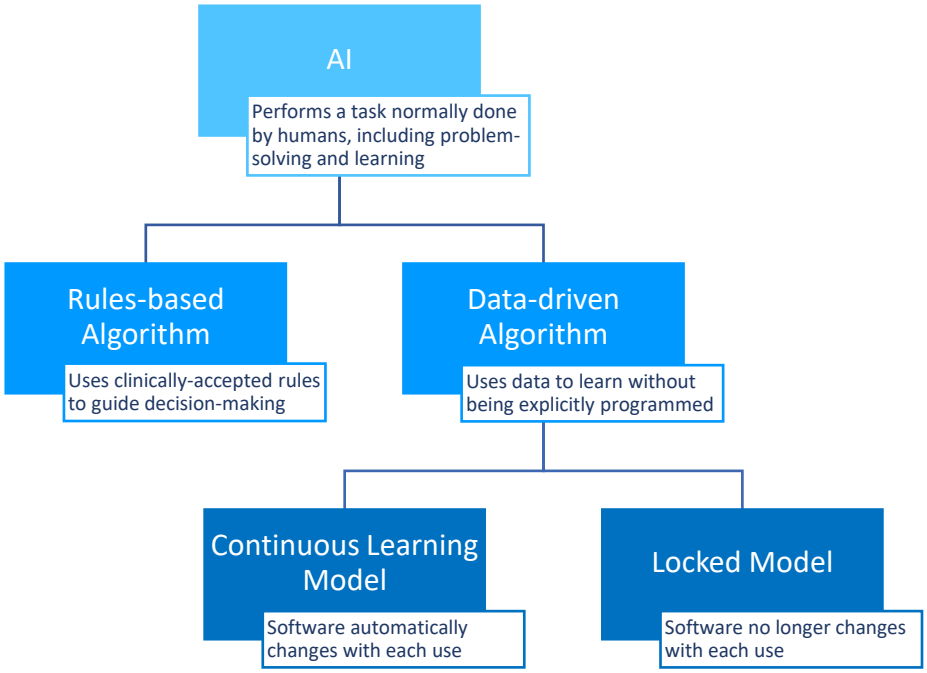

Figure 2. Types of AI Algorithm (3)

Rules-based AI is the simplest form of AI (4). From pre-existing rules, such as if-then statements or flow chart diagrams, AI systems using machine learning techniques can be automated and optimised to generate the desired output. As such, it generally performs simpler, lower-risk functions because of its high degree of transparency and interpretability. On the other hand, data-driven AI, often referred to as ML, applies algorithms to learn patterns in data without being explicitly programmed.

Once AI software developed through ML is in use, the model can continuously learn or be fine-tuned. As the software receives feedback when in use, changes can be made automatically to the function without human intervention and update the model in real time.

This process is known as continuous learning. Because of its automatic changes that may potentially impact the device's safety and effectiveness, this model poses unique regulatory challenges, risks, and benefits. How this type of continuous learning will be regulated with regards to methodological standards, ongoing verification and validation, product labelling, etc. is an ongoing discussion, and will be explored more in Section 3.

Alternatively, software manufacturers can use AI learning methods on a discrete set of training data to develop a model. Once the model is developed, it can be locked and used without automatic updates. The software can still gather the same type of feedback used in continuous learning, which software developers can then use to update the software on a regular (not real-time) basis, before following up with additional testing to understand the impact of any changes made. This is also referred to as discontinuous learning. However, if these regular updates are not done, locked models have the potential for degraded performance over time if inputs change significantly.

Lastly, AI can process two types of data: structured data, such as numerical data stored in databases, and unstructured data, such as information in text or images that require pre-processing to make sense. Since AI is contingent on data, the quality, quantity, and labelling of data has an impact on the algorithm's function output. For example, how data is labelled could lead to model biasedness, as the model learns from the human labeller's preconceptions on how to categorise patients and their features. Moreover, the model could draw skewed and biased conclusions if presented with data that is limited in scope and fails to represent the intended population.

While some computer scientists believe that human intelligence is the gold standard, AI is currently not capable of achieving that let alone replace humans. AI still needs to undergo training, a process that heavily relies on human-provided data and consultation with experts, in addition to further scrutiny and research for developers to fully understand its functionality and development. As such, most of today's industry leaders develop AI with the intention to automate repetitive and mundane tasks by modelling after human behaviour and capabilities, to alleviate the work of people and allow them to do more meaningful tasks, like patient care (5).

2.2 Why is Artificial Intelligence relevant to the healthcare industry?

Financially, AI in the healthcare market has shown much growth and promise, as the healthcare-AI market is projected to experience a ten-fold increase in size, reaching US$6.6 billion by 2021 globally (6). The use of clinical AI applications could also translate into large annual savings – by 2026, the United States (US) is predicted to cut costs by US$150 billion each year (7).

AI has an opportunity to grow in the Asia-Pacific region as well, given the region's medtech market's expected growth to be about US$133 billion for the year 2020, surpassing the European Union (EU) as the second-largest market globally (8). For example, China is predicted to be the leader of AI applications in the Asia-Pacific as its domestic market for healthcare-AI reached 20 billion yuan (US$2.85 billion) in 2018, twice that of two years prior (9). Similarly, South Korea has invested up to US$33.4 million into its domestic AI medical systems over the past three years, while the Japanese have invested more than US$100 million to set up 10 AI-enhanced hospitals by 2022 (10).

Evidently, interest in AI developments in healthcare has been growing, not just because of the financial prospects, but as a response to global healthcare and economic trends, as well as the changing needs and demands of the human population. The following are examples of healthcare trends and developments that AI developers are attempting to address:

Data Amount and Availability. With the use of electronic health records that could potentially chronicle a person's lifelong medical history and treatments, and the data generated from wearable devices or medical-related smartphone apps, the past decade has seen an explosion in the amount and availability of health data. About 80% of this extraordinary amount of data is not contained in a database or other type of data structure. Staying up to date with and accessing such data is beyond the scope of any individual human, but may be within the capabilities of AI to manage, analyse, and interpret.

Demographic and Epidemiologic Transition. With the growth of ageing populations and a more sedentary lifestyle, the global burden of disease is shifting towards long-term and chronic diseases, creating a demand for quality, preventative, and lifelong care. Asian countries are in a unique position as the region experiences the fastest rate of population ageing in the world, in addition to undergoing transitions from third world countries to first. Their healthcare systems must juggle the escalating demand for diagnosis and therapy for long-term and chronic diseases, alongside treating acute conditions and infectious diseases. Implementing versatile and artificially intelligent technology could potentially help countries adapt to a wide spectrum of situations and cope with new demands.

Demand for Precision and Personalised Medicine. As healthcare shifts its focus to preventive care of long-term and chronic diseases, the demand for more accurate and earlier diagnosis has increased as well. AI and its ability to manage and sift through big data could potentially address the demand for precision medicine, by enabling healthcare providers to develop interventions and tailor treatments best suited to individual patients based on their genomes, environment, and lifestyle.

Need to Reduce Costs and Boost Resources. Amidst the rising costs of providing quality healthcare, national healthcare systems throughout the Asia-Pacific region are also experiencing workforce shortages more acute than in countries like the US. Southeast Asia is predicted to require 12 million new healthcare professionals by 2030 (11). Industries are turning to AI to help compensate for the shortage and increase the capacity of existing healthcare workers, which could also lead to productivity gains through better diagnosis and treatment, faster drug development timelines, and self-monitoring for patients.

Technological Advancements in AI. Healthcare is currently the biggest application area for AI across industries. Considering the amount of growth and development AI has undergone, healthcare systems need to be conscious of how to navigate the application and implementation of such new technology. To apply new technological advancements safely and effectively into healthcare systems, system planners should take policy considerations into account, in addition to training of workforces, interfacing with existing systems, network requirements, and payment.

Given the changes in healthcare needs and demands as a result of changing population dynamics, technological advancements, and the wealth of personal health data, in addition to existing healthcare challenges such as manpower shortage, healthcare systems need to rethink the nature and delivery of care. With the potential for sophisticated functions such as decision-making, AI presents itself as an aid in such scenarios, allowing systems to stay relevant and keep up with novel demands.

2.3 What are some potential healthcare solutions that AI can offer?

AI's possible roles and purposes in healthcare are better illustrated by specific examples when viewed in the context of the stakeholders they can assist.

Patients: At-Home Assistance and Management. Outside the clinical setting, it is difficult for patients to be more directly involved in their own healthcare. While they may resort to searching for information on the internet, they may also lack the person-to-person guidance or health literacy on how to source for and identify reliable information. AI, in the form of a virtual health assistant, can direct patients to reliable sources based on their search history, or deliver tailored information relevant to their health situation based on their medical history, allergies, past procedures, lifestyle, and behaviours. Patients may also require help in managing their activities of daily living at home. Virtual health assistants could address this by reminding patients to take their medications or cautioning against certain foods for patients with dietary restrictions. Interactions and conversations with virtual health assistants can also be relayed to the patient's primary care physician, with details about their emotional state, questions about their treatment, or issues they are concerned about, for monitoring and

reference. Given its ability to converse and respond to a person's action, AI, in the form of "smart" robotic companions, can also provide company and alleviate loneliness to home-bound patients.

Clinicians: Augment Healthcare Workforce and Increase Quality of Care. With its potential to aid clinicians in areas like early detection and diagnosis, it is predicted that AI will augment the productivity of the existing workforce in countries like Vietnam, India, Japan, Malaysia, and Singapore by anywhere from 8% to 15%, by 2024 (12). AI can be employed to predict a person's susceptibility of developing a disease years in advance, based on patterns in data (screenings, biomarkers, risk factors etc.) too subtle for clinicians to detect. Similarly, AI can be trained to recognise lesions, tumours, or diseased areas from biopsies or x-rays and identify diseases like cancer, cardiovascular diseases, and diabetes, with the same accuracy as trained clinicians, if not more (13). By highlighting unidentified cases, AI can assist clinicians in making more accurate diagnoses and prevent patient deaths, 10% of which are attributed to diagnostic errors (14). Additionally, if AI is able to assume administrative duties like directing patients to the appropriately-skilled healthcare provider based on case severity, automatically accessing medical records on the hospital staff's behalf, or draft preliminary recommendations, hospitals can provide more efficient and better organised personal care (15).

Pharma, Biotech, and Medtech: Drug Research, Discovery, and Development. One of the earliest applications of AI has been in drug research and discovery, where AI can perform functions beyond the capabilities of researchers. For example, AI's ability to process big data makes it suitable for modelling unknown cellular mechanisms based on thousands of samples, or identify patterns between gene location, molecular function, and expression levels (16). AI can also be employed to filter through thousands of clinical trials and match patients to a programme most suited for them based on their markers, health records, and history. This helps to accelerate the search for appropriate patients as researchers race to find a cure. Utilising AI to streamline and accelerate the drug discovery and repurposing process could significantly reduce the cost to market new drugs, and save precious time for both the drug development labs and the patients relying on these discoveries.

Global Population: Tool to Monitor and Assess Population Health. AI-driven data processing methods can map the spread and burden of diseases, while AI predictive analytics can be used to project future disease spread and possible outbreaks. Risk management tools can also use AI to better understand risks across different groups of a given population and stratify these groups according to risk levels. For example, amidst the COVID-19 pandemic, AI has generated a wealth of insights by quantifying undetected infections, analysing virus mutations while being transmitted, anticipating outbreaks based on news reports from different

countries and airline data, facilitating scenario-planning for resource management, as well as predicting and identifying those most at-risk of severe complications (17). These AI-enabled tools provide value to populations, governments, and other stakeholders by enabling them to allocate their resources more effectively to prevent and manage outbreaks.

While the future of AI and the benefits it brings looks bright, it is important to remember that, given its fair share of limitations and risks that still need to be reworked and regulated, AI is not a panacea or an all-purpose solution. More importantly, AI cannot replace human empathy and is intended to work in partnership with people – by improving human decision making and enabling practitioners and researchers to work smarter, healthcare professionals are better able and equipped to deliver care with human touch (15).

3. Healthcare and Regulatory Landscape

3.1 What are some current applications of Artificial Intelligence in healthcare?

AI is increasingly sophisticated at doing what humans do, but more efficiently, more quickly, and at lower costs. The potential for AI in healthcare is vast and is increasingly becoming a part of the healthcare ecosystem in various activities (Figure 3).

This section highlights a range of companies and products to showcase AI's capabilities in drug discovery, diagnosis, early detection and prediction, patient monitoring and engagement, and ageing care, by citing examples from the US and Europe to illustrate AI's technical abilities, and examples from Asia-Pacific to highlight the latest developments in the region. More examples in other areas of healthcare can be found in Appendix A.

Figure 3. Potential applications of AI in healthcare

Drug Discovery. The path from bench to bedside is long (usually >15 years). Only 0.1% of the drugs that begin pre-clinical testing ever make it to human testing and just 20% of these

are ever approved for human use. Additionally, the average cost of developing a new therapeutic, including the cases of failed drug development, is approximately US$2.6 billion.

Despite being a costly venture, drug development has nonetheless generated a wealth of data, such as discovering molecular dynamics of drugs and their targets, and generating profiles of patients and their subgroups. AI tools could be applied to query such data to synthesise information for future clinical trials, establish useful biomarkers, run pre-clinical experiments, generate novel drug candidates, and provide insights on disease mechanisms. Incorporating AI into drug research may allow significant cuts in both time to market new drugs and their costs for drug developers, ultimately letting patients access them earlier.

Engine Biosciences, a Singapore-based technology company, is an example of pioneering network biomedicine. Their proprietary and patented technologies are oriented towards deciphering the complexity of biological networks. They include both high-throughput wet lab experimentation and AI algorithms for critical areas of drug discovery such as target discovery, drug repositioning and repurposing, and analysis of pathway and mechanism of action (18). Similarly, Hong Kong-based *Insilico Medicine* has developed a comprehensive drug discovery engine which utilises millions of samples and multiple data types to discover signatures of disease, and identifies the most promising targets for billions of molecules that already exist or can be generated de novo with a desired set of parameters (19). Such developments have been applied to study the correlations between biomarkers and ageing, to identify potential geroprotectors that can preserve a person's youthfulness and rejuvenate ageing cells (20).

US-based *Recursion* uses a "target-agnostic" approach with cell painting, whereby a biopsy sample or cell culture is bombarded with drugs and is scanned for a thousand different visual markers (21). The AI then processes this 1000-dimensional dataset to visualise the complexity of the cell's pathways and the effects drugs had on them, giving researchers greater clarity and direction on what to target after knowing the pathways available to them. Also, US-based *Atomwise* works with major pharmaceutical companies to generate data on the molecular interactions between compounds and their targets, which is then generated into an image that AI can "learn" and be trained on. Further to this, AI can aid researchers by predicting the binding affinity between future drugs and their targets based on their chemical makeup (22).

Diagnosis. Medical imaging is a rapidly growing market, generating $404 million in revenue in 2018 (23). Development in the area has been driven by the wealth of well-structured data generated by electronic health records that goes unanalysed. Looking into AI can also address the problem of high diagnostic error rates, which inevitably arise from radiologists having to review a new image every three to four seconds (24). There is also a strong potential for

clinical impact if AI can accurately identify cancer, neurological diseases, and cardiovascular diseases, allowing quick intervention for time-sensitive conditions.

With the use of medical imaging and computer vision, an AI system jointly developed by the Singapore National Eye Centre, Singapore Eye Research Institute, and National University of Singapore School of Computing, uses deep learning to differentiate between retinal images with and without diabetic retinopathy, glaucoma, and age-related macular degeneration. With its high sensitivity greater than 90% and specificity greater than 85%, it can save time for ophthalmologists and optometrists as they concentrate on the cases that need their utmost attention, allowing administration of preventive treatment early enough to curb the development of blindness (25).

In China, AI-aided medical imaging technology from the Beijing-based company *InferVISION* is being used in 260 hospitals across the country to improve the reading of CT scans and X-rays, with its ability to process 26,000 images per day to detect suspicious lesions and nodules in lung cancer patients (26). This allows radiologists to provide patients with an earlier diagnosis than is possible when sending tissue samples to a lab for analysis, thereby allowing treatments earlier than usual. Such capabilities have been put to the test during COVID-19, as doctors look through the 300 CT images generated from each patient for shadows in their lungs, a time-consuming feat as they analyse each image with the naked eye (27). *iFlytek, Yitu*, and even *Alibaba*, have also deployed AI systems at hospitals to speed up the diagnostic process, analysing CT images within 20 seconds with an accuracy rate of 90% (27,28). With software taking over labour-intensive work, overburdened staff could diagnose, isolate, prioritise, and treat patients more quickly.

Prediction & Early Detection. AI is already being used to detect diseases, such as cancers, more accurately and in their early stages, to increase the chances of successful treatment and survival. For example, US-Based *GRAIL*'s multi-cancer early detection test utilises a patient's blood sample to detect and analyse the presence of small genomic fragments released by tumour cells, to predict the likelihood of developing cancer and identify what types they may have. The use of machine learning enables GRAIL to discover patterns across multiple data points to detect cancers that cannot be identified through existing screening procedures and localise the source of the genomic fragments with high accuracy, leading to better informed diagnosis (29,30).

Similarly, a team from Massachusetts Institute of Technology and Massachusetts General Hospital developed a deep learning model that can predict, from a mammogram, the likelihood of developing breast cancer five years in advance. By training the algorithm directly on image data, instead of programming it to identify existing patterns that are

traditionally used, the system learned how to recognise minute patterns in tumour development that would go unnoticed by the human eye (31).

Apart from predicting the likelihood of cancer before it develops, AI could enable clinicians to detect potentially life-threatening conditions at an earlier, more treatable stage. For example, cardiovascular disease results in 17.9 million people deaths each year (32). While many of these lives could be saved with early detection and disease prediction, a shortage of sonographers, high costs of ultrasound equipment, and the labour intensive analysis of echocardiograms limit access to these potentially life-saving tools and analysis (33). To resolve this, *Eko.ai*, a Singapore-based medical device company, developed AI software to simplify and automate the process of manually measuring and interpreting ultrasound images of the heart. This saves time and energy for radiologists as they no longer have to sift through scans frame by frame, and allows patients to receive their results in a day (33,34).

Patient Monitoring & Engagement. AI, in conjunction with wearable devices or mobile devices that patients can use at home, can translate into more personalised and preventive care, as healthcare professionals have greater visibility of their patient's condition and lifestyle.

For example, *Biofourmis*' (founded in Singapore in 2015) variety of products feature an analytics engine that allows for continuous remote monitoring of a patient's vital signs. It receives a patient's physiological data almost in real-time via wearable sensors, and utilises AI and machine learning to draw correlations between multiple vital signs and the patient's daily activities. Based on an index computed by the algorithm, healthcare providers are alerted of any changes in the patient's condition relative to their baseline measurements, giving providers enough time to make any necessary adjustments to treatment as the disease changes (35). Different products are designed to suit different conditions, such as patients who are at risk of heart failure, experience cardiac arrhythmia, suffer from cancer, or require pain management (36). It is hoped that, by providing information on the patient's condition and by giving enough warning before an adverse event, such AI devices could reduce hospital readmissions and decrease emergency department visits (35).

Apart from monitoring vital signs, AI can encourage patients to be more involved and engaged in their health outside the clinical setting. *UneeQ*, with teams in Australia and New Zealand, developed "Digital Humans", AI chatbots that can serve as a virtual health assistant to patients recovering at home. Patients can speak to the virtual assistant at any time about any health-related topics, such as queries about their condition or side effects of medication (which the programme can recognise with computer vision), and receive answers without having to personally search for it. Additionally, when presented with questions that require professional judgment, such as whether to continue their prescriptions or not, the

programme can direct the patient to consult their physician instead and offer to make an appointment for discussion. Such conversations can also be logged and relayed to the physician for their reference, giving them greater insight into their patient's medical improvement in addition to their state of mind, allowing them to initiate more well-informed and meaningful follow-up conversations the next time they meet in person.

Ageing care. As healthcare advances with new innovations and more effective treatments, generations are living much longer than previous ones. However, that may not translate into living better, as the ageing process is often characterised by an increased likelihood of disability and prolonged suffering from age-related chronic diseases like dementia, heart failure, and osteoporosis. AI has the potential to revolutionise ageing care by helping the elderly to remain independent for longer and reduce the need for hospitalisation, caregivers, or care homes, by performing routine tasks such as taking vital signs and prompting for medication.

Developed to assist the elderly in their own homes, AI-assisted devices are also able to monitor for falls and other health parameters, and notify family members of problems. Taiwanese company, *Beyond Vision*, developed CarePLUS which consists of a 360º fisheye lens camera that can be installed into the living room ceiling, and an app for family members to monitor activities of their elderly in real-time. Apart from detecting falls and alerting family members when it occurs, machine learning enables the AI to study the elderly person's movements and alert family members when they behave irregularly, such as sitting down for too long, being in the washroom for too long, or leaving the house at unusual hours without reason (37). Such technology could give seniors and their family members greater confidence and assurance when living alone, with the knowledge that there is someone who can look out for them when needed.

3.2 What are the risk and challenges unique to the development of AI technology for healthcare?

AI has distinguished itself from existing healthcare technology because of its complexity in terms of algorithms, inputs, and outputs it processes and presents, its increased interfacing with varied types of data and reliance on data, its autonomous nature, and its capacity for continuous learning. However, such differences have unveiled unprecedented risks and amplified existing ones, namely in the realms of accountability, algorithm, process, and data, in addition to bringing ethical dilemmas and patient concerns to light (Figure 4) (38).

Accountability Risks. As the hopes and expectations for AI and its capabilities increases, it may be expected to take on tasks that require it to make and act upon its own assessments of a situation. However, such faith and reliance on AI technology can be detrimental if it makes a decision that causes harm to the patient, in which case, how does one decide where the fault may lie. The immediate reaction may be to assume faulty coding, software bugs, erroneous data, or security vulnerabilities in the programme, and hold the developers or company responsible. However, others may accuse healthcare practitioners of misusing or misinterpreting the programme, or for improper judgment if they fail to recognise the danger of the decisions made by the software. Alternatively, some may blame the regulators for allowing a faulty product to pass safety checks and be placed on the market (39,40).

Figure 4. Types of risks associated with AI (38)

AI complicates this situation with its lack of explainability. While healthcare professionals are expected to use their own judgment when using AI in their decision-making, their ability to assess the reliability and usefulness of its recommendations is hampered by the lack of technical expertise and visibility on how AI makes its decisions, further obscuring their understanding of the potential consequences of the AI's suggested plan of action (40). This lack of transparency raises an ethical dilemma as to whether medical practitioners should be expected to explain AI's "black box" nature and their lack of understanding to patients, who are then faced with the predicament of having to accept and consent to the possibility of harm due to inexplicable, technological reasons (39).

Algorithmic Risks. Considering that AI learns by independently drawing conclusions via pattern recognition and identifying correlations in data, the mechanisms and "thought process" in how it makes its assessment may be different from those of humans. While this means the

programme can find patterns and relationships that humans cannot, it also means AI could draw incorrect conclusions based on unintentional features or artefacts in data. For example, in a study testing whether one hospital's AI prediction model for pneumonia could work equally well at another, it was discovered that one of the hospital's algorithms had made its predictions based on an artefact that was characteristic of the hospital's scans, namely a metal token used by the hospital's radiologists that was captured in the top-right corner of the images it was trained on (41). Since the system itself is unable to explain to hospital staff the basis for the conclusions it makes, the risk of making conclusions for the wrong reasons needs to be monitored and accounted for.

Data Risks. With reference to the earlier example and how AI recognises patterns in data, intentionally or not, the precision, accuracy, integrity, and representativeness of training data is important. Apart from using clean data to ensure the algorithm draws correlation only from relevant measurements and factors, data has to be representative of the population and unbiased as well, or else AI could run the risk of becoming prejudiced in the healthcare system by replicating pre-existing patterns of bias in the data.

For example, an algorithm widely used by US hospitals to allocate care to patients was discovered to discriminate against African Americans, whereby they were less likely to be referred for personalised treatment despite being as ill as Caucasians. Further investigation showed the algorithm was programmed to assign risk scores based on a person's healthcare costs in a year, assuming spending was an indicator of healthcare needs. While African Americans spent an average of US$1800 less than their Caucasian counterparts, giving the impression of fewer healthcare risks and a lesser need to be referred, the algorithm failed to attribute the difference in spending to systemic issues at large, such as reduced access to care due to systemic poverty or racial discrimination by healthcare providers. By the time they are able to afford and receive treatment, they are often significantly sicker than Caucasians (42,43).

Amidst such ethical concerns regarding fair decision making by AI, it is important to recognise that AI algorithms are not deliberately programmed to discriminate against certain groups, nor is it a fault in their coding to recreate patterns of bias and discrimination inherent in population data and records. Instead, developers and healthcare professionals should be sensitive to any social biases in the training data they provide, and cognisant of their own biases when programming by incorporating minority perspectives other than their own, to ensure that algorithms make fair assessments about a person's health and their needs. Apart from identifying biases, it is also important to strive for representative data by including rare disease patients and minorities, and by accounting for inequities in healthcare due to a variety of social

determinants of health, by researching the healthcare situations of underserved populations (44).

Process Risks. While AI shows much promise and success in experimental conditions, it would be risky to assume its results can be immediately translated to a clinical setting, where it would be faced with unanticipated noise and uncertainties it was not trained for. Therefore, the software must first prove its accuracy and utility when presented with real-world data and scenarios before it can be adopted, accepted, and trusted by healthcare providers. It must also have its performance monitored to ensure consistent quality of its outputs. To help clinicians understand their performance, the software should measure and reflect metrics relevant and applicable to clinical practice, allowing clinicians to consider the safety and implications of using the algorithm's assessment (45).

One process risk, particularly relevant for predictive analytics, is model drift, whereby the initial model constructed by the algorithm is less accurate or applicable when presented with changes in the data of patient populations and disease incidence, resulting in increasingly erroneous predictions over time. For example, when predictive models for hospital-acquired acute kidney injury were presented with a decrease in the incidence rate of the disease in question, it coincided with an increase in overprediction in all models (46). As such, it is important for AI programmes to be periodically recalibrated or retrained, to prevent clinicians from making ill-advised decisions based on an imprecise prediction of disease rates.

Ethical Challenges & Need for Human Touch. Evidently, the technological challenges of AI have created ethical dilemmas by blurring the lines of accountability, transparency for doctors, and consent from patients, and has confounded reliable, safe, and fair and impartial decision making (47). Understandably, such challenges could potentially impair the doctor-patient relationship, by threatening the authority and expertise of healthcare professionals. It may also contribute to souring the patient's experience and recovery journey due to AI's lack of empathy and emotional sensitivity to social and cultural contexts, particularly in situations heavily reliant on communication, such as in nursing, delivery of unfavourable diagnoses, and managing conflicts (47,48). Because patients will be the ultimate recipients of care provided or advised by AI software, it is important to determine how much trust they can afford to put into AI, and determine the appropriate amount and significance of AI involvement relevant to the physician's (39). Ultimately, it is important to remember that despite AI's autonomous nature and myriad capabilities, it is still a tool designed to assist, empower, and work in collaboration with healthcare professionals, and is incapable of replicating the care, concern, compassion, and sensitivity that only the human touch can provide.

Apart from posing challenges unique to its programming and functionality, AI is also subjected to wider, more general risks and challenges of digital health technology (Figure 5). The following paragraphs briefly highlight a few concerns which are pertinent to AI specifically.

Figure 5. Digital health challenges of AI in healthcare

Data Availability & Ownership. Given that AI's development demands massive datasets, the quantity of data available to AI tools proves a challenge. Strong digital health infrastructures and systems are needed to provide the necessary amount of data required for AI tools. Such systems need to gather data consistently and reliably and reflect the latest in the healthcare scene, thereby enabling AI tools to stay current and identify novel health cases. Data ownership and rights to its usage are also brought into question, particularly because it is used for product development, is processed to generate insights and new information, or may be accessed from population databases and registries without patient consent.

Data Security & Cybersecurity. As AI becomes more proficient at identifying relationships and patterns between different types of data and is integrated into health systems, AI software may be granted access and channels to peripheral medical devices or patient databases to quickly receive and process the data they collect. However, this resulting Internet of Things (IoT), whereby digital devices communicate and exchange data with each other via the Internet, expands the opportunities for cyberattacks. Hackers could access AI software or patient databases by tampering with peripheral devices that may be manufactured without security in mind or built by companies that do not understand medical security requirements. From there, they may render the AI software dysfunctional and threaten patient safety or leak patients' data and compromise their data privacy. As such, a comprehensive layered approach to security is necessary to protect the healthcare network and database, including a strategy to isolate devices from other systems in the network.

Health System Integration. AI tools should be consistent with local healthcare workflows, clinical protocols and IT systems to truly provide value, efficiency, and optimisation of existing resources. However, in order to integrate with different workflows, electronic health records,

and IT systems, AI developers must either design multiple versions of the same product to suit different demands, or develop one that can adapt to various contexts. The creation of such products with a high degree of customisation would prove to be a financial challenge for AI developers, increasing their implementation costs and restricting their ability to scale up.

Additionally, such bespoke systems may pose significant regulatory considerations, as the AI algorithm may be exposed to data it was not originally programmed to process. This may result in the algorithm misinterpreting data and drawing arbitrary correlations between unrelated data sets, disabling it from functioning as originally intended. As such, the establishment of rules and guidelines on the creation of such tailored systems is necessary. However, it raises further regulatory questions, such as whether the systems manufacturer or AI developer is responsible for complying to such systems regulations, and at what point is the healthcare institution deemed to be acting as a "manufacturer" and subject to regulation when designing the system. Moreover, healthcare system planners would have to ensure they have the financial resources to purchase AI tools, the human resources and training necessary to fully utilise and accurately interpret its outputs, and the IT infrastructure to support it.

Safety, Efficacy, & Performance. The use of performance metrics can help to address risks. However, the next challenge is how to develop a standard definition of acceptable performance standards, accuracy rates, and patient health outcomes against which to measure AI. Additionally, there is debate over variability in accuracy standards across different types of AI tools. For example, epidemic predictive modelling may allow for a lower degree of accuracy than clinical decision support tools or diagnostic tools for individuals. Alternatively, some medical professionals may assert that AI tools, particularly those that provide outputs directly to patients, must always have accuracy rates equal to or greater than those of highly trained doctors, and others may argue that lower accuracy rates are acceptable for tools that provide recommendations to patients who have little access to qualified doctors or formal healthcare.

Adoption & Training. Apart from standardising performance measurements and preparing IT systems for the integration of AI, educating and training healthcare staff is equally important for its effective adoption and realisation of its value. As with anything new, learning how to use the technology may be a challenge for some. The workforce must understand what AI is and its purpose, and learn new skills and knowledge to properly utilise and interpret its outputs before they can work alongside AI and accept its presence in the workplace.

As AI shoulders some responsibilities and performs certain specialised functions, this shift will inevitably alter many of the roles of healthcare professionals. The skills required of clinicians in the future may well be markedly different from those that are needed today, as new

technology become more integrated within and across healthcare systems and more ubiquitous among the population. Therefore, an understanding of technology will be imperative, and programming, data analytics, and human behaviour may well be as much a part of the medical curricula as anatomy and physiology.

3.3 What are the existing regulations/guidelines on Artificial Intelligence in healthcare?

As AI is still in its early stages of growth, many countries lack regulations for the use of AI-enabled tools by various actors. Of the countries that do have regulations, the next challenge lies in the lack of clarity within jurisdictions and the many differences across countries or regions. This inconsistency in regulation means the protections of health and safety are lacking. Additionally, the license for AI providers to operate in a market is often highly dependent on local officials whose discretion can change quickly. This variability creates an uncertain regulatory environment that generally impedes investment and the scale-up of AI technology. Clear guidance from multilateral bodies and governments on when and where regulation of AI tools is needed is important for technology companies operating across different markets.

Over the years, several frameworks, guidelines, and white papers on AI and digital health have been issued by regulatory institutes and organisations worldwide.

The IMDRF has issued two documents, one outlining harmonised principles for the qualification and risk classification of Software as a Medical Device (SaMD), and another outlining principles for clinical evaluation (49,50). The British Standards Institution (BSI) and Association for Advancement of Medical Instrumentation (AAMI) have also convened to explore AI challenges, such as the differences between machine learning and conventional SaMD, in addition to making recommendations on how to achieve standardisation in areas such as terminology and taxonomy of AI (51–53).

The EU has established ethical guidelines on the development of trustworthy AI, in addition to publishing a white paper with proposals and policy options for the development of AI in Europe, which are applicable to digital and AI health technology (54,55).

Recognising the need to develop frameworks that are as equally flexible as AI's adaptability and constant evolution, instead of a static, one-time certification model, the US Food and Drug Administration (FDA) has focused on AI developers with its precertification program to assess the organisation's performance for high-quality software design, testing, and monitoring (56). The pilot has concluded and produced key learnings on the next iteration of testing (57). By collaborating with and trusting AI companies to uphold certification standards,

FDA can also regulate AI changes and modification as developers are expected to be transparent and update the administration when necessary (58). FDA has also been updating its catalogue of AI medical devices (AI-MD) as new innovations appear (59). The National Academy of Medicine has also recognised and identified areas in which AI can be deployed in an ethical, equitable, and transparent manner (44).

Development of the United Kingdom's regulations are currently underway, starting with discussions centred on ethical standards and guiding principles that regulations should uphold, followed by establishing standards and expectations on the various stakeholders involved in the AI product's lifecycle, issuing guidelines on the evidence of AI technology's effectiveness, and outlining ethical consideration in medical practice (39,60–62).

Across the Asia-Pacific region, there are wide variations in technology adoption, regulatory frameworks, and market sophistication in its digital health and healthcare-AI landscape. Countries like Singapore, South Korea, China, and Australia lead the way in terms of establishing the digital infrastructure and the regulatory backbone necessary to drive adoption of technology in healthcare. This can be seen by the strong penetration of digital health technology and investments into care delivery models that help to optimise health system resources and improve outcomes. The ground-breaking work done in these countries can also help guide the way for emerging markets, such as India, Malaysia, the Philippines, Indonesia, and Vietnam, which are looking at innovations that can help them achieve international care standards (63).

South Korea has focused on aiding AI-MD developers to comply with regulations, by clarifying what are considered AI-MD as opposed to more conventional medical device technology, with its detailed and multifactored classification standard and system, along with retrospective clinical trial requirement for clinical evaluation (64,65).

The Australian Department of Health, in the interest of patient safety, had amended its legislation on therapeutic goods to introduce risk-based classification rules for SaMDs, based on the type of information communicated by the software and the recipient of the information (66,67). The Therapeutic Goods Administration (TGA) has also extended their scope beyond the regulation of AI product characteristics and have focused on the regulation of importation instead, in addition to issuing guidances to better advise manufacturers on how to comply with the government's cybersecurity practices (68,69).

To accommodate the ever-evolving nature of software development and updates, China's National Medical Product Administration (NMPA) has shifted its approach from regulating a product only upon registration, to ongoing scrutiny throughout the product's lifecycle (70). After incorporating AI into its Medical Device Classification Catalog, NMPA has initiated a

standardisation unit to standardise the regulation various aspects of AI, including terminology, classification, dataset quality management (71,72). China is also one of the first countries to publish guidelines for deep learning technology (73).

Lastly, Singapore's Ministry of Health (MOH) has partnered with AI innovators, by developing a "regulatory sandbox" in which to experiment with the use of their products in a safe, controlled environment and receive feedback on regulatory approaches (74). The Health Sciences Authority (HSA) has also established regulatory frameworks to address each stage of a product's life cycle, including post-market reporting to monitor AI's use in real-world settings (75).

For further details regarding the policy and healthcare regulatory documents mentioned, and more, a summary table is provided in Appendix B (last updated October 2020)**.**

3.4 What are some regulatory concerns to consider when developing regulations/guidelines on Artificial Intelligence in healthcare?

While regulatory agencies may never develop regulations faster than the advancements of technology, it is still necessary to develop and implement targeted strategies in a timely manner before the challenges and risks of technology becomes too pervasive. Rather than being reactive, regulators should take a novel and forward-thinking approach to regulations, to anticipate and prepare for future challenges.

Taking reference from the aforementioned regulatory frameworks and guidelines, the following section highlights important regulatory concerns, and details how some existing regulations and guidelines address them.

Qualification of SaMD. Among the wide range of AI tools and software designed to serve a health-related purpose or be used in a clinical setting, not all of them may be considered a medical device subject to regulation. Clearly qualifying whether an AI application is a medical device as defined in law or regulation or not allows regulators to focus their attention and resources on software that presents the highest or most immediate risk to patients and/or users.

For example, IMDRF recommends qualifying or regulating software based on whether it serves a medical purpose, which includes but is not limited to: diagnosis, prevention, monitoring, treatment, or alleviation of a disease or injury; investigation, replacement, modification, or support of the anatomy or a physiological process; or supporting or sustaining life (49). Currently, US FDA, the EU, and Singapore's HSA have substantially adopted this approach.

Singapore has also clearly specified that software "intended for general wellbeing purposes or serves to encourage or maintain a healthy lifestyle" with no intention for any medical purpose (such as detection, diagnosis, monitoring, management or treatment of any medical condition or disease) would not be treated as a medical device (76). HSA then requires developers of such products to issue a clarification statement that the device should not be used for diagnostic purposes, to allow consumers to make informed and responsible decisions when interpreting and acting upon the device's output. Apart from excluding the function of maintaining or encouraging a healthy lifestyle, the US further narrows the qualification of SaMD by excluding devices that serve the purpose of administration, and act as digital health records, including those that transfer, store, convert, or display data and results (59).

Risk Classification. Considering the many roles and functions AI can play, the implications and effects they may have on decision making will present a spectrum of risks, which may become more or less significant depending on the severity of the situation. Good regulatory practices dictate that regulatory controls should be proportional to the level of risk presented. For example, IMDRF uses two major factors, namely the significance of information provided by the software to healthcare decision which depends on its intended use, and the state of healthcare situation or condition (Table 1) (49). Similarly, HSA's risk classification changes with functionality, where displaying or triaging data poses a low risk, while predicting disease progression or delivering/modifying treatment poses the highest.

Table 1. IMDRF's SaMD Risk Classification (49)

Status of Healthcare situation or condition	**Significance of information provided by SaMD 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

Clinical Evaluation. Monitoring and mitigating risks attributed to AI's outputs can be done in conjunction with evaluating the software's clinical application and performance. To achieve this, IMDRF has issued a guidance document outlining the necessary steps to clinically evaluate SaMD commensurate with the risk it poses. IMDRF focuses on three areas – valid clinical association, analytical validation, and clinical validation – to ensure that not only is the software producing accurate, reliable, and precise outputs, but that it is of value and applicable to the condition or context it is intended to address (50). The United Kingdom health

technology evaluation body adopts a similar approach by first classifying digital health technology by function followed by stratifying them into evidence tiers, based on the potential risks they pose to users. Apart from helping to identify technology that poses higher risks, it has also organised and specified the type of evidence required to prove a product's effectiveness, depending on which tier it is in (62). HSA has also adopted the approach of stratifying the clinical evidence required based on the risk stratification for software medical devices (75).

Human Intervention. Depending on the functions performed by the AI-MD, the amount of human intervention exists along a spectrum as well, depending on how much of the decision making is performed by the clinician or the AI. For example, diagnostic tools that highlight information in images or test results have a high degree of human intervention, as the doctor can choose what to do with that information and makes the final clinical decision. Conversely, diagnostic tools that analyse the data and generate a diagnosis independently without involving a doctor's assessment have lesser or no human intervention. The amount of agency and decision-making power held by the AI software will affect the risks it may pose and the potential severity of consequences in the event of error, and therefore requires proportional precautions to safeguard those involved.

In Singapore, the structure and elements of future AI guidelines drafted by the Ministry of Health (MOH) specify the importance of identifying AI risks in an institutional setting, and implementing the appropriate amount of human oversight regarding its use. HSA also requires AI developers to clearly indicate the degree of human intervention and the stage(s) of intervention in the product's workflow, as part of their submission for pre-market registration (75).

Learning Models, Change Management & Alternative Regulatory Pathways. The ability to "learn" and change with experience makes AI software distinct from other SaMD. This can be a challenge to regulate, as the product may no longer be the same as when it was first authorised for marketing, and may develop new, unforeseen hazards. However, the amount and nature of change within the product depends on whether it utilises a rules-based model, data-based locked model or continuous learning model, as outlined in section 2.1.

Generally, a rules-based model is low risk since it is based on existing decision-making guidelines which could be represented as a flow diagram, giving it a high degree of transparency and interpretability. Locked models have a fixed function that is applied to a given set of input data, meaning that when the same input is presented, it is likely to return the same result. While it appears to be static in nature, its performance may degrade if left

unchecked, and requires manual updates and validation of its algorithms to ensure it continues to work as originally planned.

Continuous learning models may prove to be the most challenging, as it automatically changes with time and adapts itself depending on the situations it encounters. Compared to the locked model, AI may provide different results over time even if the inputs are similar. Not only would the AI medical device be different from what it once was, it would also be vastly different when comparing the same product that has been deployed in differing hospital systems and contexts, complicating its regulation. Given that the initial validation would no longer be applicable once the algorithm is faced with and adapts to new scenarios, manufacturers need to implement measures and risk management systems to ensure continued safety and performance even as the model changes.

Regardless of the model, modifications by the manufacturers, such as retraining with new and current data or patches to the programme, are inevitable to improve and keep AI software up to date. However, since updates may impact the AI's performance and quality, and thereby the patient's safety, change management protocols, such as a change notification process, and open communication between manufacturers and regulatory agencies are necessary to review the significance and monitor the effects of such changes. For example, in Korea, where depending on the scale and impact of the change, such as whether it is a change to the AI's training data within the approved range, bug fixes, change in user interface, or change in principle of operation, manufacturers need to seek approval from the Ministry of Food and Drug Safety (MFDS) before proceeding (77). Similarly, NMPA determines the significance of a software update depending on whether the change influences the safety or efficacy of the software, involves changes to the algorithm structure, or involves updating of training data that would statistically change algorithm's performance (78).

Furthermore, the US FDA has proposed a framework that can be applied to continuous learning models, whereby the developer has to outline the changes they plan to achieve when the device is in use, as well as the methods they will use to achieve and appropriately control the risks of the anticipated modifications they outlined (58). Similarly, HSA requires manufacturers to submit a well-defined change management methodology and monitoring system as part of their quality management system, to ensure no new issues are introduced and the algorithm continues to work as intended (75).

Post-Market Monitoring. Lastly, post-market monitoring is necessary to support to pre-market requirements, not only to ensure the safety and efficacy of the AI software in real-world settings, but to also be vigilant and prepared for unforeseen adverse events. HSA requires manufacturers to undertake a variety of activities, namely mandatory reporting of serious

adverse events or field safety corrective actions so HSA can ensure appropriate rectifications have been made, cybersecurity surveillance to ensure a timely response to unforeseeable and evolving threats, maintaining traceability and reporting of the deployment of significant version updates to HSA. Additionally, manufacturers are required to monitor the real-world performance of AI and submit periodic reports post-deployment for HSA to monitor their continued safety and effectiveness.

In addition to the areas detailed above, other areas worth investigating would be:

- Quality of data: to ensure data that it is trained on and validated by is relevant to its intended use to produce quality outputs, ensuring the model works correctly as intended
- Transparency, interpretability & usability: to ensure the system is not only understandable for its intended users, but also performs as it should when used by its intended users
- Risk management: to ensure continued reliability and safety of both continuous and locked models in areas where AI may introduce new hazards
- Real-world performance: to ensure the software continues to work as intended and perform as expected, while real-world data is collected and utilised for its continued development

3.5 What are some recommendations for the Asia-Pacific Region to move forward?

To the extent that AI-based healthcare technologies fall within the ambit of “medical devices” subject to regulation, existing general regulatory principles and international harmonisation guidance documents issued by organisations such as IMDRF, GHTF, AHWP, and ASEAN, along with current national medical device regulations in some countries, generally form an appropriate foundation for their effective regulation. It is important to recognise that these regulations will require supplementation with more detailed and specific guidance documents to address issues specific to AI. Topics include: software design and validation, their dynamic and adaptive natures and dependence on data, data integrity, and systems integration. The effective implementation of such regulations and guidance also heavily depends on a country’s regulatory capacity, resources, expertise, and infrastructure to effect such change and sufficiently protect public health.

As technology continues to rapidly evolve, it will be important to periodically review the appropriateness and effectiveness of such regulations and guidance. Good regulatory practices, such as those outlined by OECD or the ASEAN Guidelines on Good Regulatory Practice (e.g. transparency, regional cooperation, promotion of stakeholder engagement and

participation, and being open to regular review for continued relevance, efficiency, and effectiveness) continue to be applicable to build capacity for AI regulation (77). Some AI-based healthcare technologies will fall outside the scope of existing medical device regulatory frameworks e.g. those not directly intended for use in diagnosis or therapy, and policy makers will have to consider the need for appropriate alternative regulatory systems for such products.

Work should be done to resolve challenges specific to AI, for example, data privacy, post-market monitoring and real-world evidence, and international standards. Such work requires the collaboration and incorporation of perspectives from national regulatory agencies and AI developers, in addition to government agencies, healthcare providers, and standard development organisations like the International Organisation for Standardisation (ISO) and International Electrotechnical Commission (IEC), to design effective regulations that balance safety with innovation.

While data privacy may be beyond the scope of regulators traditionally concerned with safety, performance, and quality, there is a need to ensure that AI can gather, access, and process clinical or health data, while safeguarding confidentiality and patient privacy. One possible step is to distinguish between personal and non-personal data, depending on the purpose of the AI device and the data it utilises. For example, AI software trained to detect cancer may process personal data to generate a patient's profile, but the key data they analyse would be the cancer biomarkers or pixels from an image scan, which in itself do not contain information that can be traced to an individual. By separating the two types of data into different databases, regulators can require the implementation of stricter security controls to personal data specifically, while allowing AI developers and their software to access non-personal data in a way that does not compromise privacy (78). Such a solution would also require cooperation amongst government agencies and compliance to government policies on data collection, to ensure informed consent is obtained and patient privacy is protected, when data was first collected in a clinical setting and until it is stored and utilised by AI.

When exposed to real-world settings and data, the outputs of AI have the potential to evolve in ways that neither AI developers nor regulators can wholly anticipate. Therefore, regulations should require monitoring of product performance after marketing authorisation. They should also ensure the software continues to perform safely, effectively, and consistently as expected, regardless of the environment or inputs they receive. Effective, corrective, and preventive action systems, as part of the manufacturer's quality management system, should be linked to post-market monitoring. Changes in product performance, especially those beyond any foreseen in the original marketing authorisation application, may also require further verification and amendment to the original marketing authorisation.

Implementing such monitoring and surveillance systems will require collaboration among regulators and AI developers, and users as well. One possibility is for NRAs to host consultations with developers, similar to the current practice of HSA. Not only would this serve as an opportunity for developers to learn the necessary regulations and medical practices they need to comply with, but regulatory agencies can also understand what is feasible on the ground for developers and manufacturers. Apart from hosting consultations with AI developers, NRAs can bolster their regulatory capacity by developing access to the expertise of consultants and academic experts specialising in AI-based healthcare technologies, who can provide guidance on policy making and help resolve questions in premarketing evaluation, post-market vigilance, and performance monitoring.

An important element of many existing national medical device regulatory systems and international harmonisation guidance is the use of recognised voluntary, national or international, norms and standards. Compliance with such standards is an established means by which the developer or manufacturer may demonstrate that its product conforms to relevant regulatory requirements and the current "state of the art". Current international consensus general standards such as IEC 60601 for electromedical device safety, IEC 62304 for software lifecycle processes, ISO 14971 for risk management, or ISO 13485 for quality management systems are widely used and important building blocks. However, they are not specific to AI-based healthcare technologies. There is a need to develop new sector-specific standards to supplement the general standards. Recognition of international standards by NRAs forms an important element of regulatory capacity building as it reduces the need for each authority to have detailed expertise, and because standards reflect a consensus view of good practices and requirements. The widespread recognition of standards is also an enabler of regulatory reliance inasmuch as it promotes confidence in the work of other regulators and a shared basis of understanding. As AI-based healthcare technologies continue to mature, the participation of regulators and healthcare providers, along with technology developers, should be encouraged.

Lastly, as AI developers and regulators work to promote and protect the health and safety of patients, it is important to provide a platform for patient representatives to be heard as AI products and regulations are developed. Although patients are often consulted during product development for the purposes of studying their healthcare needs and user experience, patient groups could also be involved in discussions on regulations. This will help them be aware of the purposes, limitations, benefits, and risks AI poses, along with the safeguards regulatory agencies are putting in place. Patient groups can share their opinions, concerns, priorities, and address what they are willing to consent to when receiving healthcare recommended or provided by AI. Such discussions are also a good opportunity for AI developers and regulators

to remember that while AI has the potential to solve a multitude of healthcare problems, it is no replacement for empathy and the human touch, and that the patient is at the heart of healthcare.

4. Conclusion

AI technology has unveiled some promising new solutions with the potential to help healthcare systems navigate a volatile, uncertain, complex, and ambiguous healthcare landscape. However, AI-based technology must first prove its safety, efficacy, and value in real-world settings by demonstrably improving public health, both at individual and at population levels. AI developers must collaborate with researchers, healthcare professionals, and patients to design products that end-users can understand and fully utilise. Similarly, as AI developers implement preventive and monitoring measures to mitigate risks in the event of failure, users need to be clear on AI's roles and functions, and learn how to safely use and interpret the software's outputs to optimise its potential benefits.

Furthermore, regulatory frameworks and digital health infrastructure in medical institutions must not only be restructured to facilitate interoperability between AI technology and other digital health devices or systems, but also have the flexibility to adapt and evolve alongside AI's own development and evolution. AI developers, regulatory bodies, and healthcare institutions will have to discuss policies regarding data integrity, governance, accessibility, validity, and quality to ensure AI technology operates on representative, unbiased, and updated data. Medical practice will also evolve and redefine medical education and professional regulation as healthcare providers require a new set of skills.

Countries in the Asia-Pacific region have been progressing at different rates and implementing their own health product regulatory frameworks to meet their society's needs. If the region intends to strengthen its healthcare landscape through the adoption of AI-based technology, regulatory leaders must address these challenges collectively and prospectively, to promote regulatory harmonisation, set the standards of good regulatory practices, and lay firm foundations for future regulatory activities. Regulations would have to be impartial with a sound, legal basis that can be applied to all actors consistently and fairly, yet with enough flexibility to accommodate evolving technology. Regulations must have clarity and transparency for informed decision making, and be efficient and effective in their use of public resources to achieve high degrees of public health protection.

Author

Ms Micaela Leong Hui Jin

A/Prof Silke Vogel

Dr Nokuthula Kitikiti

Mr Ananda P Muthalagu

Centre of Regulatory Excellence

With Contributions From

Prof John CW Lim

Mr Michael Gropp

Centre of Regulatory Excellence

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Appendix

Appendix A: Additional Examples of Applications of AI in Healthcare

Disease Research. While drug discovery is one of the earliest areas for the application of AI, it has to work in concert with research into the diseases they intend to treat as well. AI can play a pivotal role by accelerating and enhancing genomic sequencing, model diseases, and streamline patient recruitment for clinical studies.

To create a comprehensive overview of how a disease manifests and progresses from a cellular level, it is necessary to first understand the underlying genomics of the disease by mapping out the cell's gene expression and characterising the relationship between cells (81). AI can assist in such research and provide greater specificity when sequencing genomes. For example, while next-generation sequencing can inform scientists how the majority of cells behave in a given tissue, *10x Genomics*, with its AI technology, is capable of sequencing the genome of each and every individual cell and provide higher resolution analysis. Such specificity is of great advantage in oncology, where tumours are an amalgamation of various cell types. By providing information about rarer tumour cells instead of just the majority, oncologists and researchers can broaden the search for novel drug targets, and develop treatments for rarer but more persistent cell types (82).

Apart from researching disease pathology, AI has also been applied in disease modelling because of its ability to process large longitudinal datasets and draw correlations between various types of measures, which may not be immediately apparent to epidemiologists or mathematicians. With enough data from a variety of sources beyond public health data, AI could predict when and where outbreaks will occur, even on the other side of the world. For example, *BlueDot*, a Canadian AI firm, were aware of the COVID-19 outbreak in Wuhan, China, days before official notifications from the World Health Organisation or US Centres for Disease Control and Prevention. They achieved this by using an AI algorithm that searched for foreign-language news articles, plant and animal disease networks, and airline data, and created a model that was better at simulating disease transmission compared to one generated solely on public health data (83). While the accuracy and usefulness of such models ultimately depends on the quality of data, the ability to model and predict transmissions allows governments, airlines, and hospitals to take precautionary measures to isolate the spread of infections at its origin, or even help plan the allocation of resources in the event their people are affected.

AI can help streamline disease research by improving the efficiency of patient recruitment. The sheer number of clinical trials available is difficult for patients with rare diseases to sift

through, as not only do they have to find one that addresses their condition, they also need to assess if they fulfil the trial's requirements based on their markers. The use of AI can help streamline this search based on a variety of factors, be it a person's biomarkers and medical history to match them to a trial most suitable for them.

Conversely, patient recruitment may be difficult simply because the targeted group of patients are unaware that such clinical trials exist. Researchers can utilise AI that analyses internet users' conversations and behaviour to locate potential participants. *IQVIA*, a solutions provider in the realm of data science in human health, was able to use its AI-based social media listening software to locate the various platforms that online individuals and communities use to discuss psoriasis in the Southeast Asian region. Alternatively, health information websites like *Hello Health*, a Southeast Asian equivalent of websites like WebMD or Mayo Clinic, can serve as a potential pool for eligible participants with the use of targeted advertising. IQVIA's AI solution can be programmed to analyse a person's usage and behaviour on the website, such as the symptoms, treatments, or topics they search for and the articles they click on, to create a profile of the person and their condition. After this, the website's algorithm can advertise clinical studies that may be relevant to their condition, raising awareness about the existence of such trials they can participate in.

Diagnosis. In addition to analysing medical images generated from CT scans or X-rays, AI could assess physical injuries. Singaporean start-up *KroniKare* diagnoses wounds with a portable multi-spectral scanner that allows quick scanning of a patient's chronic wound, followed by carrying out AI analysis for each wound scanned. This server has been fed with data from over 15 years of clinical experience in chronic wound support and can cross-check the scanned wound against existing information in under a minute (84). A report is generated by the AI technology and takes additional data that has been manually keyed in by nurses or on-duty healthcare practitioners into account.

AI could also potentially provide psychiatrists and psychologists a more accurate screening and assessment for cognitive disorders such as Attention Deficit Hyperactivity Disorder (ADHD). Accurately diagnosing ADHD may be difficult, particularly in the Asian context, as parents' and teachers' judgments of what is normal behaviour expected from a child is steeped in cultural expectations and lifestyle (85). For example, a child's failure to meet high academic standards characteristic of an Asian education system, may be misinterpreted as a learning disorder.

As such, the use of an AI programme developed by the University of Texas at Arlington may be of help, where their machine learning system assess a child's behaviour while performing physical and computer exercises for any patterns of inattention, hyperactivity, or impulsivity

characteristic of ADHD (86). Similarly, the University of Buffalo developed a mobile app that can detect autism in children with 94% accuracy by tracking their eye movement when presented with pictures featuring multiple people, to determine if they exhibit eye movements characteristic of someone with or without autism (87). With timely screening and more accurate diagnosis, psychiatrists may have an easier time identifying children most in need of treatment and intervention to better cope and adjust as they grow up.

Early Detection & Prediction. Apart from utilising AI to detect diseases such cancer or heart conditions, AI has the potential to identify mental health disorders, with the use of natural language processing in conjunction with machine learning.

While still in its infancy with limited capabilities, AI has the potential parse complex human behaviour such as speech and language, to predict the risk of developing mental health disorders. Such tools could be useful in the Asia-Pacific region where many are deterred from getting diagnosed and resort to suffering in silence, because of the lack of mental health literacy and fear of social stigmatisation in Asian cultures (88). In a research study conducted in Cincinnati, USA, enrolled patients were classified as suicidal, mentally ill but not suicidal, or neither. Each patient then completed standardised behavioural rating scales and participated in an interview with open-ended questions. When the machine learning algorithm was presented only with their verbal and non-verbal data, it could correctly classify the patients and differentiate between each group with up to 93% accuracy (89). With further training, the algorithm could help healthcare providers identify suicidal behaviour early enough for patients to receive counselling and reduce the incidence of suicides.

Decision-Making. After making diagnoses or early predictions, the next step for AI is to make decisions and propose intervention treatment. With information on the person's risks and likelihood of developing a medical condition or a trajectory of the development of their disease, as derived from their markers and how it matches with patterns in real-world data, AI could offer suggestions tailored to the person's situation. For example, US-based *Tempus*' AI-driven clinical decision support tools, used in concert with their molecular sequencing services that measures for tumour biomarkers, generates a comprehensive report of the patient's status. This report contains key indicators measuring the development of mutations in tumour cells that can be translated into patient care, alongside suggestions on actionable treatments derived from real-world evidence from millions of other patients (90). By providing insight on the progression of the patient's tumour, in addition to offering treatment options relevant to the patient's status, physicians have greater visibility of the options available to them to make the next appropriate step.

Alternatively, AI could help pharmacologists deepen their understanding of the effects and outcomes of a targeted treatment by running simulations. *Onkolyze*, a recent Singaporean biotech start-up, developed an AI-based breast cancer diagnostic assistant for decision support to radiologists, by making use of biological experiments and computer simulations to model outcomes for individual patients. The probable outcomes of different treatment strategies can be estimated for individual patients *in-silico* prior to administration, and could support the radiologist's decision to personalise the optimal therapeutic strategy for individuals (91).

Another Singaporean start-up, *Bot MD*, developed an AI assistant for clinicians integrated in an app, which can instantly answer questions regarding the hospital's call rosters, drug formulary, guidelines, and protocols (92). Convenient access to guidelines and protocols can quickly inform healthcare providers of the appropriate course of action during stressful scenarios, while knowledge of the stocks, resources, and specialists available can inform providers of the available treatment, solutions, and manpower at their hand.

Administration & Accessibility. Apart from serving clinicians and specialists, AI can alleviate the workload of hospital administrators and nurses as well, by taking over laborious manual processes such as bed allocation. Tan Tock Seng Hospital, Singapore's leading geriatrics centre, experiences high occupancy and strain despite increasing bed capacity by 30%, given the demands of the country's growing elderly population (93). The implementation of an AI algorithm runs through 300 rules to provide the best recommendation on the allocation of beds, and helps prioritise admissions of critically ill patients. The use of unique RFID tags to their bed number also coordinates other activities upon being discharged, such as updating the bed management unit, issuing billing, and activating housekeeping, allowing smoother and more efficient hospital and patient management.

In large nations like China, AI can improve accessibility to quality healthcare, and help the country's network of tiered hospitals better manage resources. China's public hospitals are stratified into three tiers: Tier 3 hospitals are large and well-equipped with comprehensive facilities while Tier 1 hospitals are in rural areas with smaller facilities and less well-staffed. As tier 1 facilities are challenged by the lack of well-trained or licensed doctors and nurses, many patients to turn to Tier 3 hospitals instead for better quality care, putting a strain on their resources. *Baidu*'s AI-based Clinical Decision Support System (CDSS), which is able to recognise symptoms of 66 diseases, was designed to help Tier 1 hospitals better address the demands of their local areas. After its implementation, the staff's capacity, service quality, and credibility increased, encouraging patients to visit them instead of higher-level hospitals (12).

Similarly, *Ping An Good Doctor* piloted its AI-powered booths known as “One-Minute Clinics”. In it, patients can communicate their symptoms to an AI doctor, which then relays the patient’s medical history and a proposed diagnosis to an in-house clinician for them to connect with the patient remotely. The clinic is also stocked with a smart medicine cabinet of 100 common medications that can be dispensed after diagnosis (94). Such clinics in remote areas could improve the population’s access to medical care in spite of China’s shortage of doctors, with 1.8 for every 1,000 people (95).

Treatment & Disease Management. AI can help clinicians take a more comprehensive approach for disease management to better coordinate care plans. It can also help patients to better manage and comply with their long-term treatment programs or provide a virtual coach.

For example, *Meracle*, a Singapore-based start-up, developed digital health technology to address suboptimal medicine delivery in chronic diseases such as asthma therapy. Their product, the Whizz Spacer, improves the management of asthma by increasing the efficiency of medication delivered into the lungs while tracking intake data to augment the assessment of treatment outcomes. The virtual assistant also sends reminders to the patient to trigger their administration of the medication and includes a rewards system to incentivise the young population to take the treatment consistently (96).

Other companies tackle long-term and chronic diseases with digital health technology incorporating AI. *Health2Sync* (Taiwan) provides a smart companion for glucose control. The app transforms the data recorded by the patient into useful information, and helps in finding the most suitable diabetes management method, as well as communicates with the care provider (97). *Wellthy Therapeutics* (India) also provides a smartphone-based lifestyle management program for people with diabetes (98).

Susmed (Japan) developed Yawn, a medical app to treat insomnia through cognitive behavioural therapy. Sessions are based on data entered by the patient, such as sleep status and daytime activities. An AI-powered algorithm then analyses the patient’s state and delivers personalised advice automatically through a chat program (99). On a similar model, *Naluri* (Malaysia) combines behavioural science and data mining to build mental resilience for chronic disease patients (100).

Perx (Australia) is another example. It tackles the issue of treatment compliance, regardless of the disease. The platform combines an engaging app experience with real rewards to remind and motivate users to adhere to their treatment plan. Participants in the program earn prises by completing their scheduled tasks, participate in challenges, gain useful insights into their habits, and discover the wider Perx community (101). Following the same trend, *AiCure* (United States) has built an application to monitor patients with long-term conditions and help

them adhere to their medication regimen. The app uses a visual recognition system to identify the patient's face, the medications they are taking, and confirm ingestion. The data is then sent back to the care provider, or to a pharmaceutical company conducting a clinical trial (102).

Wellness & Prevention. Lastly, one of AI's potential benefits is to help people maintain or improve their health, reducing the likelihood of developing diseases and need to consult a healthcare provider. By educating users on the changes they can make in their own lives to inculcate healthy habits, these applications can encourage healthier behavior in individuals and help them proactively manage a healthier lifestyle.

One example is *Wysa*, an "emotionally intelligent" AI chat application based in India and the United Kingdom, designed to address the lack of knowledge on mental wellness and inaccessibility to emotional help. Apart from serving as a safe space for users to talk about their stress, anxiety, or feelings, it also teaches techniques for emotional regulation, such as mindfulness, meditation, or positive thinking, based on the conversation it has with the user (103,104). An application like this can educate and engage the public to practice good practices for their emotional and mental wellbeing in times of need, regardless of whether they are diagnosed or not.

Posture 360 (a company based in South Korea) is another example. It has built integrated posture products embedded with sensors that alert the person about their posture. The seamless integration of wearables and software provides suggested posture corrections, and includes digital analytics for end-users to benefit from personalised coaching offered by health professionals (105).

Lastly, health insurers, such as *Prudential*, are also getting involved in developing AI algorithms for preventative healthcare, by developing an AI-powered health and wellness ecosystem for its customers. The platform integrates four other healthcare applications to serve as a one-stop source for all healthcare needs, providing AI symptom checking and risk assessment, doctor referment and virtual consultation, and wellness coaching and physical activity tracking. With such tools readily available, users can conveniently identify any medical issues they have, receive follow-up and treatment, and monitor their health day to day, encouraging them to engage in and take ownership of their health with convenience (106).

Ageing Care. AI also enables robots to go even further by having conversations and socially interacting with the elderly to keep their minds sharp, in addition to combatting loneliness and isolation characteristic of this stage in life. PARO is one example of an advanced interactive robot developed by *AIST* (based in Japan), designed as pet therapy for seniors with dementia. Shaped as a baby harp seal, it allows the documented benefits of animal

therapy to be administered to patients in hospitals and extended care facilities where live animals present treatment or logistical difficulties. Research has shown its ability to reduce stress, anxiety, and antipsychotics use, on top of stimulating and improving socialisation among the elderly population and with their caregivers (107).

Appendix B: Summary Table of Policy and Regulatory Documents by Organisation or Country

Regulatory Document	Summary of Document
IMDRF	
Software as a Medical Device (SaMD): Possible Framework for Risk Categorisation and Corresponding Considerations | IMDRF, September 2014 (49)	1. Establishes harmonised vocabulary when qualifying SaMD based on the medical purpose it performs 2. Establishes risk classification based on significance of information provided by SaMD, and severity of situation/condition it is being applied in
Software as a Medical Device (SaMD): Clinical Evaluation | IMDRF, September 2017 (50)	1. Highlights actions needed to clinically evaluate SaMD (valid clinical association, analytical validation, and clinical validation)
BSI & AAMI	
The Emergence of Artificial Intelligence and Machine Learning Algorithms in Healthcare: Recommendations to Support Governance and Regulation | BSI, AAMI, 2019 (53)	1. Characterises AI and its challenges, highlights areas requiring further investigation (e.g. terminology & categorisation, validation, accountability, product life cycle, cybersecurity, healthcare landscape) 2. Drafts recommendations for future standardisation activities (e.g. terminology & categorisation standard, validation processes guidance etc.)
Machine Learning AI in Medical Devices: Adapting Regulatory Frameworks and Standards to Ensure Safety and Performance | BSI, AAMI, Early 2020 (51,52)	1. Expands upon previous paper by examining differences between ML and traditional SaMDs 2. Suggests collaboration with IMDRF to establish working group to standardise terminology, map existing AI-applicable international regulatory standards to IMDRF's Essential Principles to identify gaps 3. Intends to develop guidance on factors affecting data quality, validation to assure product quality, and develop criteria for deployment in healthcare systems as part of evaluation protocol
European Union	
Ethics Guidelines for Trustworthy AI |European Commission's High-Level Expert Group on AI, April 2019 (54)	1. Explicitly states trustworthy AI should be lawful, ethical, robust 2. Seven key requirements for AI to achieve this: empower and incorporate human agency, minimise and prevent unintentional harm, respect privacy and data protection, transparency for informed decision making, fair and unbiased, awareness of its societal and environmental impact, accountable
On Artificial Intelligence - A European approach to excellence and trust | European Commission, February 2020 (55)	1. Proposes policy framework with measures aligning efforts at regional, national, and European levels, to achieve "ecosystem of excellence" by

	mobilising resources along entire value chain and creating right incentives to accelerate adoption of AI solutions 2. Support for human-centric approach, to be achieved by complying with EU rules on the protection of fundamental rights and consumer rights, to create “ecosystem of trust”
United States	
Digital Health Software Precertification Programme | FDA, January 2019 (56)	1. Programme aims to have tailored, pragmatic regulatory oversight that assesses organisations for transparency and product performance across SaMD's lifecycle, and verifies continued safety, effectiveness, and performance in real world setting 2. Developed based on trust that companies continue to develop high-quality products that meet standards they are expected to uphold
Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) | FDA, April 2019 (58)	1. Proposes framework to hold developers accountable for transparency by updating FDA on changes, and ensure real world performance 2. Introduces "predetermined change control plans" during premarket submission, includes anticipated modifications and method to implement changes in controlled manner ("algorithm change protocol") 3. Acknowledges changes can come in forms of performance, input, and intended use, the last of which necessitates restarting approval process
Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act | FDA, September 2019 (59)	1. Outlines exclusion of certain software functions and uses from definition of SaMD (administrative support, maintenance/encouragement of healthy lifestyle, serves as electronic patient records or transfers, stores, converts, displays data and results)
Updated Guidances on the Regulation of Digital Health Technologies | FDA, October 2019 (108)	1. Clarifies FDA's interpretation of 21st Century Cures Act, namely on Clinical Decision Support, which broadens to patient decision support software and not limited to healthcare professionals 2. Updates on 6 guidance documents to ensure alignment with new approaches adopted by FDA (mobile medical applications, general wellness devices, medical device data systems, image storage devices and image communications devices, use of off-the-shelf software)
Artificial Intelligence in Health Care: The Hope, the Hype, the Promise, the Peril | National Academy of Medicine, 2019 (44)	1. Identifies and address various topics related to the ethical, equitable, and transparent deployment of AI in an effort to prioritise trust, equity, and inclusion in the use of AI in healthcare

Developing the Software Precertification Program: Summary of Learnings and Ongoing Activities | FDA, September 2020 (57)	1. Summary of learnings that have arisen as a result of testing processes with pilot participants e.g. mock Excellence Appraisals, mock Streamlined Review packages 2. Highlighted areas for further exploration e.g. how to help manufactures define SaMD products consistently with IMDRF framework, collection methods for ongoing Real-World Performance data etc. 3. Outlines next steps to iterate and revise testing approach to refine various aspects of program
United Kingdom	
Code of Conduct for Data-driven Health and Care technology | Department of Health and Social Care, September 2018, Updated July 2019 (60)	1. Outlines 10 principles expected from suppliers of data-driven technology 2. Establishes expected behaviour from those developing, deploying, using data-driven tech, to ensure abidance of ethical principles (respect for persons, respect for human rights, participation, accounting for decisions)
The Future of Healthcare: our Vision for Digital, Data and Technology in Health and Care | Department of Health and Social Care, October 2018 (61)	1. Sets clear standards on use of technology in healthcare, centred on 4 guiding principles (user need, privacy and security, interoperability and openness, and inclusion); outlines architectural principles to achieve this 2. Describes necessary changes to be made to revamp digital healthcare system
Artificial Intelligence in Healthcare | Academy of Medical Royal Colleges, January 2019 (39)	1. Summarises the practical, ethical, and clinical implications of AI in the healthcare system, namely in the areas including, but not limited to: patient safety, doctor-patient relationship, public acceptance and trust, accountability for decisions, inequality and fairness, data consent and information governance
Evidence Standards Framework for Digital Health Technologies | National Institute for Health and Care Excellence, March 2019 (62)	1. provide classification guidelines by function and different evidence tiers 2. establishes standards for the evidence of effectiveness of digital health, to demonstrate their value in the healthcare system 3. intended for AI using fixed models; standards for adaptive models outlined in Code of Conduct for Data-Driven Health and Care Technology
South Korea	
Guidelines on Classification of Medical Devices with Artificial Intelligence Technology | Ministry of Food and Drug Safety (MFDS), June 2017 (64)	1. Proposes preliminary approval screening method for products that integrate AI technology and guidelines for rapid commercial introduction 2. Defines MD classification standard and system related to license screening, clinical validity verification method, learning data management,

	change permission/authentication methods, permission screening application form
Guideline on Clinical Evaluation of Validity for Artificial Intelligence Medical Devices | MFDS, July 2018 (65)	1. introduces retrospective clinical trial requirement to verify effectiveness, suggests change management measures during clinical trials
Australia	
Regulation of software, including Software as a Medical Device (SaMD) | Australian Department of Health, TGA, February 2019 (68)	1. Proposes reforms to existing regulation of SaMDs to rectify issues of: classification rules that do not adequately considers potential risks some SaMD can pose to patients, lack of monitoring of product safety and performance and post-market accountability as users can download SaMD directly from publisher, lack of clarity in regarding requirements for demonstration of safety, quality, performance
Medical Device Cyber Security Guidance for Industry | Australian Department of Health, July 2019 (69)	1. Guidance for manufacturers and medical device sponsors responsible for supplying MDs regarding potential cyber threats arising from the Internet of Things 2. Advises manufacturers and suppliers on how to embed improved cyber security practices and follow risk-based regulatory approval pathways in line with government's regulations and cyber security strategy
Therapeutic Goods Legislation Amendment | Australian Department of Health, TGA, July 2019 (67)	1. Introduces new classification rules according to potential to cause harm through provision of incorrect information; largely aligned with software rules of the EU Medical Device Regulation of 2017
Ethical Principles for Artificial Intelligence in Medicine | Royal Australian and New Zealand College of Radiologists, August 2019 (109)	1. Outlines 9 principles to guide the development of professional and practice standards, regarding the deployment of machine learning systems and AI tools in medicine 2. Principles specifically designed to address the development of standards and research practices, regulation of market access, development of standards and practices in deployment, upskilling of medical practitioners, and ethical use of such tools in medicine
China	
Medical Device Classification Catalog | NMPA, August 2018 (71)	1. Includes AI-assisted diagnostic tools to medical devices classification system 2. Only certified companies/products can charge for their services; other products within law's framework can conduct clinical trials for free in hospitals to provide evidence to NMPA for certification

Creation of the Medical Device Standardisation Unit | NMPA, March 2019 (72)	1. initiation of a standardisation unit for the purpose of standardising terminology, classification, dataset quality management, basic common tech, quality management system, product evaluation, and special evaluation methods for AI medical devices
Technical Guideline on AI-aided Software | NMPA, June 2019 (73)	1. Guidelines developed to address characteristics of deep learning technology, focuses on control of software data quality, ability to generate valid algorithms, and clinical risks 2. Clarifies naming convention of software updates to algorithm and data, and companies are to list all typical scenarios for major updates; minor updates managed internally
Singapore	
Licensing Experimentation and Adaptation Programme – Regulatory Sandbox Initiative | MOH, August 2018 (74)	1. Regulatory sandbox initiated to better understand variety of new innovations, care and business models by partnering with industry players 2. Provides developers space to innovate and explore healthcare delivery to patients in a safe and controlled environment; opportunity to provide feedback on regulatory approaches
Structure and Elements of Future AI Guidelines | MOH, November 2019	1. Key principles for developers and implementers requires AI to be explainable, transparent, fair; patient-centric; lawful and accountable 2. Guidelines structured to parallel product journey: design and development, implementation, and monitor and review 3. Highlights considerations regarding end-user's understanding, safety and bias, continuous care, integration into clinical workflow, performance monitoring
Regulatory Guidelines for Software Medical Devices – A Lifecycle Approach | HSA, November 2019, updated April 2020 (75)	1. Product lifecycle approach to regulation; takes into consideration amount of human intervention and learning model 2. developers required to clearly define AI's intended and expected purpose + functionalities, input data, performance specs, control measures i.e. monitoring + detection of outliers 3. Post-market monitoring and reporting required from developers as well (e.g. mandatory reporting after adverse events, real-world performance monitoring post-deployment, etc.)

Contact us

Tel: +65 6601 5147
Email: CoRE@duke-nus.edu.sg

Duke-NUS Medical School
8 College Road
Singapore 169857
www.duke-nus.edu.sg/core

centre-of-regulatory-excellence

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