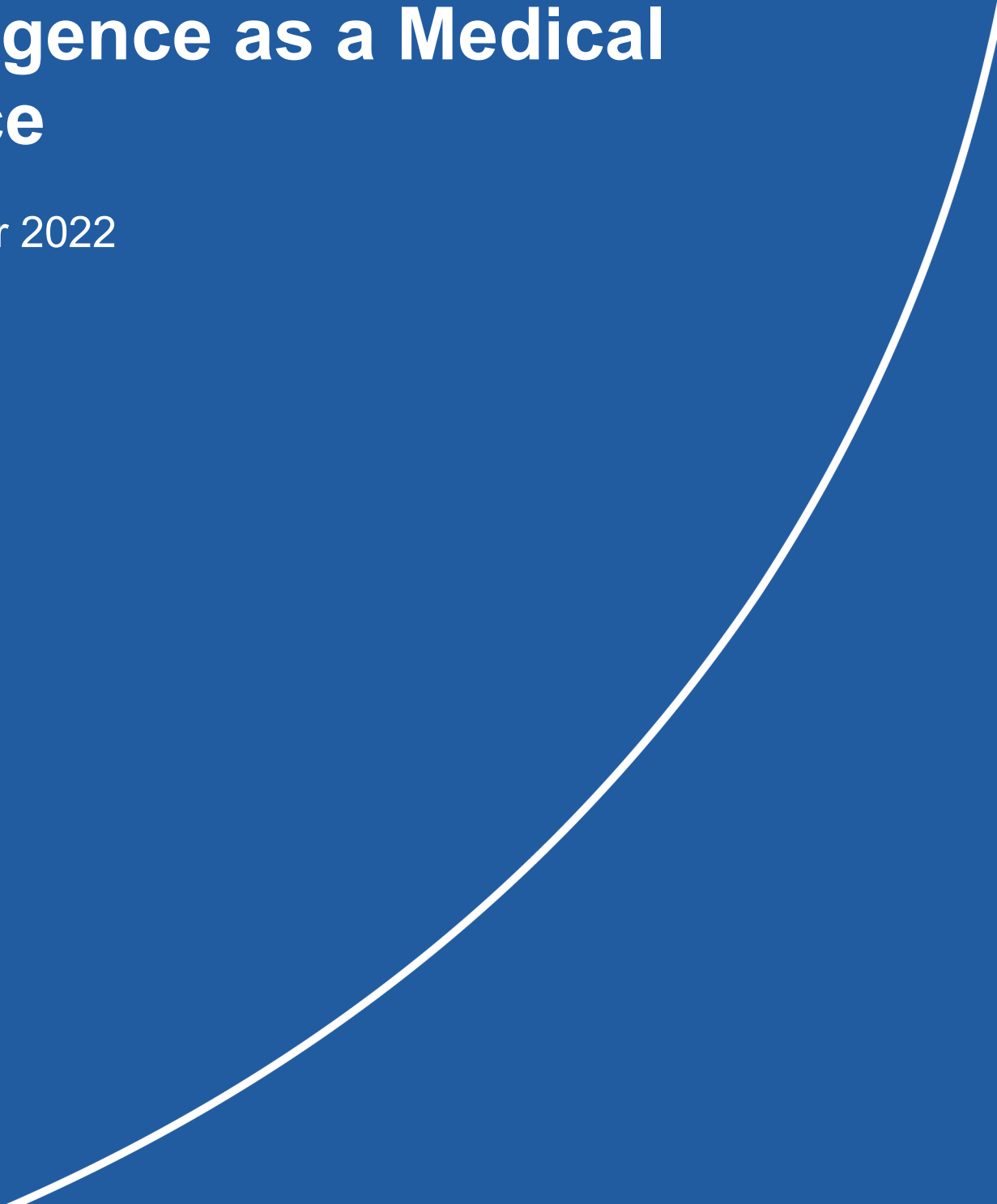


REGULATORY
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The Regulation of Artificial Intelligence as a Medical Device

November 2022



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Foreword

Lord Darzi of Denham

As a clinician and leader within the NHS for more than thirty years, I am proud to be part of a service that brings together all our knowledge, skills and care to improve the health and well-being of the people of the UK.¹ The challenges are perhaps greater than at any time in our lives: the primary shock wave of the Covid-19 pandemic, and the secondary shock waves of neglected chronic illnesses and negative impacts on staff and health service capacity, all in the context of increasing institutional and individual financial pressures. In the face of such challenges, we cannot simply do more of the same. This is true for the NHS, and true for health services across the world. If we are to deliver excellent care, and to do it affordably, then we all need to innovate and evolve.



Digital technologies – and in particular those that can allow us to automate complex processes – are critical to our future healthcare. This ‘Tilt to Tech’² includes medical devices that are enabled by ‘artificial intelligence’ in which the technology can undertake tasks that would normally require human skills: identifying abnormalities on cross-sectional imaging to detect lung cancer, detecting and classifying retinopathy in people with diabetes, predicting outcomes so as to guide treatment decisions. Such tools can free up staff to focus on what we need them for most – the things that can’t be automated, such as communicating the implications of a serious diagnosis, or discussing the pros and cons of a complex treatment decision. However, for the things that can be automated, AI health technologies have the potential to provide 24-7 services with a quality, reliability and speed that exceeds even the best human performance.

How do we unlock this opportunity whilst also ensuring that such technologies are safe? This largely depends on getting the regulation right. The regulatory framework for these devices needs to be *efficient* and *sufficient*. Excessive regulation will block innovation, preventing patients and the health service from benefitting from the improvements in healthcare, and would hold back UK companies in this sector. Conversely, inadequate regulation could allow unsafe (or biased) technologies to come to market, potentially exposing the UK population to medical devices that may do them harm.

This Regulatory Horizons Council report provides a timely analysis of the UK’s current regulatory framework of AI as a medical device (AIaMD). It recognises areas that are working well (or where identified needs are already being addressed), but also highlights gaps in the current framework.

¹ Darzi A. Department of Health. High Quality Care for All. NHS Next Stage Review Final Report. 2008. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/228836/7432.pdf

² Darzi A. Institute for Public Policy Research. Better Health and Care for All: A ten point plan for the 2020s. The Lord Darzi review of health and care. 2018. Available at <https://www.ippr.org/files/2018-06/better-health-and-care-for-all-june2018.pdf>

Drawing on the breadth of their multi-stakeholder consultation, best international practice, and deep experience of the sector, the Council have provided specific recommendations that are actionable and would create a regulatory framework for AIaMD that would support patient safety, and make the UK one of the most attractive places for AIaMD innovation in the world. The report benefits from being led by someone who is not only an expert in the evaluation and regulation of these devices, but is himself an NHS clinician. Prof Denniston and the Council team have ensured that this review is grounded in the reality of today whilst also being ready for tomorrow. I am delighted to welcome this report as it seeks to ensure that we unlock the benefits of these technologies for patients in the UK and beyond.

Lord Darzi of Denham

Paul Hamlyn Chair of Surgery at Imperial College London and the Institute of Cancer Research; and

Co-Director of the Institute of Global Health Innovation, Imperial College London.

Former Parliamentary-Under-Secretary of State for Health 2007-2009

1. Executive Summary

Artificial intelligence (AI) - the use of machines to do complex tasks that we associate with human intelligence – is one of the most exciting areas of development in health, with potential benefits across a wide range of applications from faster diagnosis to the prediction of pandemics, from clinical decision support to digital therapeutics.³ The aspiration of technological solutions with super-human performance, free of human error and inconsistency, and scalable at will to provide expert-level care across health systems is highly attractive, particularly in the context of stretched health systems across the world.

In a UK context, health strategies such as the NHS Long Term Plan increasingly identify the use of AI health technologies as a key approach to meet increasing demand, improve efficiency and to enhance quality.⁴ The UK government has invested significantly in this sector, for example through the £140M NHS AI Health and Care Award which has funded a wide range of AI health technologies at different stages of development, with a view to accelerating innovation and bringing these technologies into routine use. Technologies funded through this award include screening systems for diabetic retinopathy and breast cancer, and GP triage systems, which are now under active evaluation for use in the NHS.⁵ In a global context, the market for AI health technologies is expected to expand at a compound annual growth rate of 38.4% from 2022 to 2030 to reach USD 208.2 billion by 2030.⁶

Although there has been rapid development in AI health technologies, with an increasing number achieving regulatory approval and being marketed in the UK as medical devices, there is concern that we do not yet know how to ensure effectiveness of these technologies, or how best to detect, analyse, report, and act upon errors and potential harms that can arise from their use. There is very little evidence as to their safety when deployed outside of pilot studies or at scale, and little consensus as to how this safety should be assured. Given that many AI health technologies are designed to be used at scale (for example in national screening programmes), a failure to detect and mitigate potential errors could cause harm at population level which may not be detected for months, years, or at all.

There is an urgent need – and an exciting opportunity - to get the regulation right for AI as a Medical Device (AIaMD). Getting it right is about ensuring that the regulatory system is ready for these technologies. It is about benefiting patients with early access to high quality AIaMD technologies, confident that they have been demonstrated to be effective, safe and equitable and are continuing to be monitored. It is about benefitting the UK health technology sector (including

³ Topol, E.J (2019) '[High-performance medicine: the convergence of human and artificial intelligence](#)' Nature Medicine 25, 44–56

⁴ NHS Long term plan (2019). Available at:<https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf>

⁵ <https://www.england.nhs.uk/aac/what-we-do/how-can-the-aac-help-me/ai-award/>

⁶ [https://www.researchandmarkets.com/reports/5351653/artificial-intelligence-in-healthcare-market?utm_source=BW&utm_medium=PressRelease&utm_code=q5tlj6&utm_campaign=1728628+-+Global+Artificial+Intelligence+in+Healthcare+Market+\(2022+to+2030\)+-+Size%2c+Share+and+Trends+Analysis+Report&utm_exec=jamu273prd](https://www.researchandmarkets.com/reports/5351653/artificial-intelligence-in-healthcare-market?utm_source=BW&utm_medium=PressRelease&utm_code=q5tlj6&utm_campaign=1728628+-+Global+Artificial+Intelligence+in+Healthcare+Market+(2022+to+2030)+-+Size%2c+Share+and+Trends+Analysis+Report&utm_exec=jamu273prd)

manufacturers and supply chains), to accelerate innovation, enabling them to bring high quality AIaMD products to market faster, to efficiently gather performance and safety data in the post market phase, and to regularly (or even continuously) update AIaMD to optimise performance. There is an opportunity to create a regulatory environment for AIaMD that would be internationally-leading in its ability to support innovation, with wide-ranging benefits to the health and wealth of the UK.

Our report also highlights the need for regulation of AIaMD to consider the specific risks that the use of AI brings, such as differential performance of AI health technologies, and the risk of ‘AI bias’ against marginalised groups including ethnic minorities. Common reasons for this bias include under-representation of that group within the training and testing datasets (‘health data poverty’) and the encoding of human biases into the data. We must ensure that any new AI regulatory framework ensures ‘safety for all’ and not just ‘safety on average’.

Whilst the focus of this report is very clearly on AIaMD, it is also important to recognise the wider regulatory landscape for medical devices which has been highlighted by the 2020 Independent Medicines and Medical Device Safety Review led by Baroness Cumberlege,⁷ and the 2021 Regulatory Horizons Council Report on Medical Devices.⁸ The findings (and recommendations) of those reports remain valid, and a number of them are so essential to AIaMD regulation that we have emphasised them again here. The recent MHRA Consultation on Medical Devices also highlighted some of the challenges of medical devices generally, and Software as a Medical Device (SaMD) and AIaMD in particular. The Government response to that consultation noted that these now had ‘applications in health and social care that could not have been envisioned when existing regulations around medical devices were developed, and it is anticipated that these applications will continue to increase in coming years’.⁹ The Government response and the publication of the MHRA’s ‘Software and AI as a Medical Device Change Programme Roadmap’ contain a number of proposals that are clearly relevant, and form part of our consideration here.¹⁰ Throughout the report we also acknowledge several important measures that are currently being developed by key organisations working in the sector, and which should be supported and built on as key building blocks in the creation and delivery of an internationally-leading regulatory framework for AIaMD.

⁷ Baroness Cumberlege (2020), *Independent Medicines and Medical Devices Safety Review*: https://www.immdsreview.org.uk/downloads/IMMDSReview_Web.pdf

⁸ Regulatory Horizons Council (2021), *Report on Medical Devices Regulation*: <https://www.gov.uk/government/publications/regulatory-horizons-council-report-on-medical-devices-regulation>

⁹ Consultation on the future regulation of medical devices in the United Kingdom (2021). Available at: <https://www.gov.uk/government/consultations/consultation-on-the-future-regulation-of-medical-devices-in-the-united-kingdom>

¹⁰ <https://www.gov.uk/government/publications/software-and-ai-as-a-medical-device-change-programme/software-and-ai-as-a-medical-device-change-programme-roadmap>

Where do we want to be?



1. A regulatory system with the **capacity, capability and agility** to deal with increasing demand and emerging challenges in AIaMD



2. A regulatory framework that ensures that AIaMD are **safe, effective and equitable** throughout their product life-cycle



3. A regulatory framework for AIaMD that is **open and transparent, actively involves patients and the public,** and provides **clarity** for manufacturers and users



4. A regulatory framework that positions the UK as an **international leader** in patient safety and innovation in emerging technologies in medical devices such as AIaMD

Summary of RHC recommendations: Bridging the gap in the regulation of AIaMD

Theme: There is an urgent need to increase regulatory capacity and capability to address the immediate needs of the growing AIaMD sector and the healthcare system with regards to patient safety and innovation.

Recommendation 1: The MHRA should be specifically resourced with a long-term funding commitment to enable them to create and service a regulatory framework that is efficient, proportionate and safe, and supports the UK in being a leader in the innovation, evaluation and utilisation of AIaMD.

This could be achieved by:

- a) Providing a longer-term settlement for the MHRA to specifically resource and accelerate the essential Change Programme for SaMD/AIaMD, and then to make sure they retain and grow high calibre individuals with the unique skills and knowledge who can deliver this;
- b) Ensuring that wider government recognises the importance of SaMD/AIaMD as a driver for UK innovation, growth and patient benefit, whilst also recognising that this will only be realised if the regulatory system is proportionate and adequately resourced; and
- c) Ensuring that the wider MHRA and DHSC strategy recognises the distinct needs of regulation of AIaMD (and medical devices more generally) and where this differs from the regulation of medicines, and ensures that expertise in devices is represented at Executive level within the MHRA.

Recommendation 2: Strengthen regulatory capacity and capability in AIaMD addressing pre-market and post-market phases, through targeted training of regulators and other gate-keepers and key contributors across the total product life-cycle.

This could be achieved by:

- a) investing in training in AIaMD, SaMD and medical devices to build capacity within the MHRA and other relevant UK regulators, ABs, regulatory consultancies, and manufacturers;
- b) strengthening expertise in known and emerging issues within AIaMD amongst all relevant gate-keepers (MHRA, NICE, HRA, CQC, health institutions) sufficient to enable them to provide the necessary level of scrutiny of such devices and their usage within their scope of influence; and
- c) Educating and creating capacity for relevant staff groups within the NHS so that they are confidently able to play their part in the safe deployment of these devices, and recognise their critical role in assuring patient safety.

Theme: There is a need for the UK to create a regulatory framework that considers the whole product life-cycle to ensure that AIaMD are safe, effective and equitable

Recommendation 3: The UK should aim for an AIaMD regulatory framework that is 'legislatively light' and maximises the role of standards and guidance and builds on existing regulations for SaMD whilst also addressing the specific challenges of AI technologies.

Recommendation 4: Manufacturers should be required to provide evidence that they have evaluated and mitigated risks of the two major issues of (1) poor generalisability and (2) AI bias that can arise due to the use of AI.

This could be achieved by:

- a) Manufacturers recognising the specific risks of *poor generalisability* in AIaMD, and putting in place processes to evaluate and mitigate them;
- b) Manufacturers recognising the specific risks of *bias and selective under-performance* in AIaMD, and putting in place processes to evaluate and mitigate them;
- c) MHRA requiring this evidence to be included in the technical file provided to the AB, and available for onward sharing to relevant bodies with a patient safety remit; and
- d) Relevant downstream regulators and gate-keepers (e.g. NICE, CQC, and health institutions planning to deploy these technologies) requiring this evidence as part of their assessments.

Recommendation 5: Manufacturers should provide information regarding the extent to which the basis of the outputs of the AIaMD is interpretable and can be interrogated.

This could be achieved by:

- a) Manufacturers seeking to maximise the extent to which an AIaMD may be interpretable, and the outputs can be interrogated;
- b) MHRA requiring this to be reported transparently in the intended use statement or other supporting documentation as part of the human-computer interaction and to support error analysis as part of safety monitoring; and
- c) Relevant downstream regulators and gate-keepers (e.g. NICE, CQC and health institutions planning to deploy these technologies) requiring this information to support their requirements for post-market surveillance.

Recommendation 6: The regulatory framework should support innovative mechanisms that enable accelerated access with more evidence generation occurring after deployment.

This could be achieved by:

- a) A coherent multi-agency Innovative Devices Access Pathway for technologies that are recognised as being high-priority for the NHS and with sufficient existing safety data to support an expedited approach;
- b) Increasing resourcing and capacity for the Multi-Agency Advisory Service (MAAS) to provide end-to-end regulatory advice for AIaMD manufacturers;
- c) The MHRA providing a 'provisional registration' mechanism for appropriate technologies; and
- d) NICE recognising an 'early deployment' route within its Evidence Standards Framework for Digital Health Technologies.

Recommendation 7: Prior to a local deployment, manufacturers should work with health institutions to provide evidence that the AIaMD is likely to perform safely within their local setting, and work with them to provide that evidence where still needed.

This could be achieved by:

- a) Manufacturers working with health institutions to provide evidence of generalisability, including in external settings that resemble the local setting and population; and
- b) Manufacturers working with health institutions to assess performance and safety on previously collected data from within that setting, or undertaking a silent trial using prospectively collected data but without influencing patient care.

Recommendation 8: Key stakeholders including NHS, regulatory agencies (MHRA, CQC), and manufacturers should work together to create standards that ensure that post-market monitoring of performance and safety should be pro-active, systematic and an essential condition of deployment.

This could be achieved by:

- a) Key stakeholders – including NHS, regulatory agencies (e.g. MHRA, CQC), and manufacturers - working together to create systems that provide efficient, business-as-usual systems for monitoring performance and assuring safety of AIaMD, such as through a *medical algorithmic audit* approach including subgroup analysis and identification of 'failure modes';

- b) The MHRA requiring Approved Bodies (ABs) to share all performance and safety data provided to the AB regarding an AIaMD whether from pre-market conformity assessment, or through post-market follow-up or other post-market surveillance activities, and for the MHRA to hold this centrally to support their own and other relevant UK regulators' efforts in supporting patient safety;
- c) The NHS and regulatory agencies being resourced to build multidisciplinary teams that can undertake the design, maintenance and evolution of these systems in line with an acceleration of AIaMD, and to invest in training and creating capacity for new types of professional (including clinician, technologist and regulator) to support this work;
- d) The Government continuing to resource and support the NHS Transformation Directorate's Data for R&D Programme to build NHS-hosted Secure Data Environments (SDEs) that can support near-real time monitoring of safety by the relevant health institution and manufacturer working together, and to which regulators would have access as needed; and
- e) Research funding being made available to support the piloting and evaluation of these safety monitoring systems within the NHS, taking a regulatory science approach that supports evidence-based policy.

Recommendation 9: In addition to safety monitoring, stakeholders should work together to create systems in which AIaMD performance can be optimised through model updating and innovation within a secure data environment of the NHS.

This could be achieved by:

- a) The MHRA working with key stakeholders, including Approved Bodies and Manufacturers, to create a Predetermined Change Control Plan (PCCP) mechanism that enables AIaMD to be updated to optimise performance without compromising safety;
- b) Requiring manufacturers to pre-specify the performance and safety thresholds at which their AIaMD model would require retraining, specifying these thresholds and the mechanism of retraining as part of their technical submission (and/or PCCP) to the AB;
- c) Funding further cross-disciplinary research into how to define, detect, predict and respond to significant change in performance for an AIaMD;
- d) Utilising the SDE-based safety infrastructure described earlier (Recommendation 8) to not only provide monitoring for safety purposes but to also enable manufacturers to efficiently update models to optimise performance (and correct for any drift in performance); and
- e) The Information Commissioner's Office (ICO) providing guidance to health institutions on legal and governance issues relating to how they may provide access to anonymised, participant-level data to manufacturers and regulators for the purposes of safety monitoring and optimising performance of AIaMD.

Recommendation 10: The health institution and device manufacturer should be required to agree, as part of contractual negotiations prior to deployment, an approach for monitoring and responding to performance and safety issues that adequately assures patient safety and ensures that there is a 'Plan B' in case of the need for device withdrawal.

Theme: There is a need to make the regulatory process for AIaMD more open and transparent, increase involvement of patients and public, and improve regulatory clarity for manufacturers and users

Recommendation 11: The end-to-end regulatory pathway for AIaMD needs to be clearly communicated, and supported by guidance that is accessible to innovators that are new to medical device regulation and with adequate explanation for public and patients to have trust in the system

This could be achieved by:

- a) The key regulators and gate-keepers (MHRA, NICE, CQC, and health institutions) developing coherent approaches with a common language; and
- b) Using joint mechanisms such as the Multi-Agency Advisory Service to provide shared materials and consistent advice to users.

Recommendation 12: Regulatory processes for AIaMD should have adequate explanation for public and patients to have trust in the system, which should be supported by the MHRA providing a public-facing register to include all AIaMD on the UK market, including their risk class, their intended use statement and a plain English summary of their intended use statement.

This could be achieved by:

- a) The key regulators and gate-keepers (MHRA, NICE, CQC, and health institutions) developing public explainers of regulatory guidance and documentation; and
- b) The MHRA creating a searchable public-facing register for SaMD (or AIaMD) that have been registered on the UK market, including as a minimum their risk class, their intended use statement and a plain English summary of their intended use statement.

Recommendation 13: Manufacturers, regulators and other stakeholders should demonstrate and role model greater patient and public involvement in the design, evaluation and regulation of AIaMD.

This could be achieved by:

- a) Manufacturers including patients and the public in problem selection, design choices and user testing, with a particular emphasis on engaging with users of the relevant healthcare pathway; and

- b) Regulators and gate-keepers (MHRA, CQC, NICE, and health institutions) including patients and the public more effectively within their decision-making processes.

Theme: There is an opportunity for the UK to demonstrate leadership in innovation and patient safety by pursuing international harmonisation

Recommendation 14: The UK should demonstrate international leadership in the regulation of AIaMD, leveraging its expertise and position to support international harmonisation in this area.

This could be achieved by:

- a) Supporting the MHRA in their new role as full member of the International Medical Devices Regulators Forum (IMDRF) programme, and resourcing them to contribute to both the Medical Device Single Audit Program (MDSAP) and the proposed Medical Device Single Review Program (MDSRP); and
- b) Supporting and resourcing the MHRA and UK experts from across sectors (standards bodies, industry, academia, clinical) to contribute to the development of international standards and guidance for AIaMD.

Recommendation 15: The UK should aim for regulatory efficiency in AIaMD governance by adopting good reliance practices in medical device regulatory decision-making.

This could be achieved by:

- a) Early adoption of unilateral recognition with appropriately aligned jurisdictions (for example the USA and EU) so as to reduce friction on medical device imports, and ensure that patients within the NHS and wider UK continue to have access to the medical devices they need; and
- b) Longer-term investment in developing mutual recognition agreements with these jurisdictions to enhance exports and reduce the burden on UK manufacturers.

2. Introduction

The Regulatory Horizons Council (RHC) is an independent expert committee that identifies the implications of technological innovation, and provides Government with impartial, expert advice on the regulatory reform required to support its rapid and safe introduction. The area of AI in health was identified both in the RHC's original horizon scanning exercises in 2020,¹¹ and recurrently through the stakeholder engagement exercises conducted as part of the 2021 RHC report into Medical Devices.¹² Cross-sector consultation was then conducted to define the scope and review questions with a view to ensuring that any review addressed areas of AI health technologies where regulatory reform could be most beneficial. With this in mind, this report focuses specifically on AI as a Medical Device (AlaMD), and the urgent need for regulatory reform in this area if the UK is to be a leader in the innovation and utilisation of effective, safe and equitable AI in healthcare.

This report was led by Alastair Denniston with support from Parag Vyas on behalf of the RHC¹³ and supported by a team of Civil Servants within BEIS. The report was informed by a broad programme of stakeholder engagement (outlined in [Annex A](#)).

What is AI as a Medical Device (AlaMD)?

In broad terms, a medical device is 'an article, instrument, apparatus or machine that is used in the prevention, diagnosis or treatment of illness or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for some health purpose'.¹⁴

A subset of medical devices comprise standalone software or software included in wider hardware and are known as Software as a Medical Device (SaMD). More recently, AI approaches are being incorporated into SaMD, and these may be described as AlaMD (see Figure 1).

The AI component of AlaMD may be variable in complexity and significance. Broadly AI may be defined as *'the science of developing computer systems which can perform tasks normally requiring human intelligence'*.¹⁵ Example use cases for AlaMD are outlined in Box 1. It should be noted that when people refer to AlaMD – including those interviewed for this report - they are usually focused on a further subset of those devices that use Machine Learning (ML); as noted by

¹¹https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949318/potential-priority-areas-for-the-council.pdf

¹² Regulatory Horizons Council (2021), Report on Medical Devices Regulation: <https://www.gov.uk/government/publications/regulatory-horizons-council-report-on-medical-devices-regulation>

¹³ RHC membership details are here: <https://www.gov.uk/government/groups/regulatory-horizons-council-rhc#membership>

¹⁴ https://www.who.int/medical_devices/definitions/en/

¹⁵ Liu, X et al (2020). Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. *Nature medicine*, 26(9), 1364–1374. <https://doi.org/10.1038/s41591-020-1034-x>

the IMDRF such devices may be more precisely described by the term ML-enabled Medical Devices (MLMD).¹⁶ For the purposes of this report, we will stick to the familiar term AIaMD, but highlight any ML-specific issues at the relevant point.

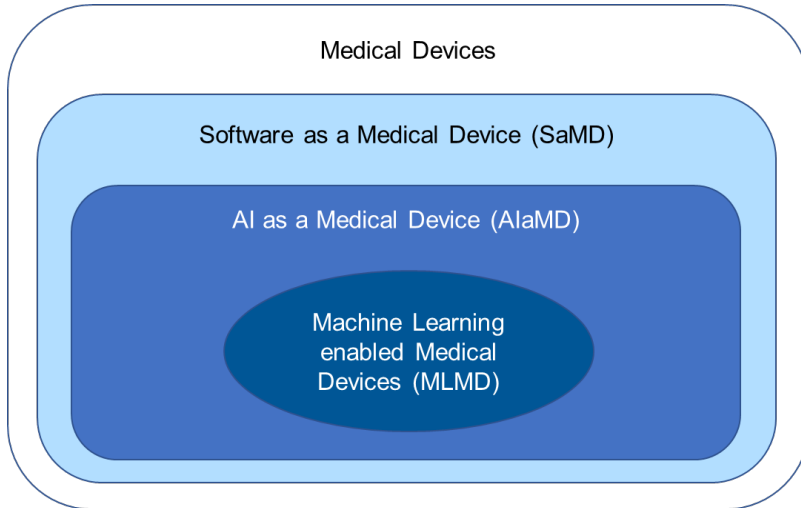


Figure 1: Diagram illustrating the relationship between Medical Devices, Software as a Medical Device, AI as a Medical Device and Machine Learning enabled Medical Devices.

¹⁶ <https://www.imdrf.org/documents/machine-learning-enabled-medical-devices-key-terms-and-definitions>

Box 1: AlaMD Use Cases

Most medical devices deploying AI can be categorised into one of three broad use categories: diagnosis and screening, prognosis and supporting treatment.

Diagnosis and screening – A common application for AlaMD is in diagnosis and screening programmes.¹⁷ For example, IDx-DR is an AlaMD that analyses retinal images taken as part of screening programmes for people with diabetes. It was the first autonomous diagnostic system to be approved in the USA and is one of several AlaMD for diabetic retinopathy now in use around the world. These are potentially valuable tools to detect and prevent blinding complications of this increasingly common condition.¹⁸ For cancer screening, AlaMD have been developed that detect a range of early cancers on scans, for example detecting early cancers on mammograms^{19 20} or on chest X-rays.²¹ AlaMD are also being used to support endoscopists detect abnormal polyps²² and pathologists identify cancerous cells from biopsy samples.²³

Prognosis – AlaMD may be used to evaluate a patient’s risk of developing a particular outcome, for example the risk of developing a new condition, or the risk of developing a specific complication of a known condition. In these cases, the AlaMD integrates multiple inputs – for example personal risk factors (genetic, lifestyle), previous medical history and relevant tests, and then predicts the outcome based on this data. This can then be used to provide more personalised care to that individual. For example, having accurate information on the likelihood of developing a heart attack can help in deciding when to start medication for lowering blood pressure and cholesterol, and may help a patient make decisions about lifestyle issues such as diet and smoking cessation.

¹⁷Liu, X. et al (2019). A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: a systematic review and meta-analysis. *The Lancet. Digital health*, 1(6), e271–e297. [https://doi.org/10.1016/S2589-7500\(19\)30123-2/](https://doi.org/10.1016/S2589-7500(19)30123-2/)

¹⁸ <https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-artificial-intelligence-based-device-detect-certain-diabetes-related-eye>

¹⁹ Morgan, M. B et al (2021). Applications of Artificial Intelligence in Breast Imaging. *Radiologic clinics of North America*, 59(1), 139–148. <https://doi.org/10.1016/j.rcl.2020.08.007>

²⁰ McKinney, S. M et al (2020). International evaluation of an AI system for breast cancer screening. *Nature*, 577(7788), 89–94. <https://doi.org/10.1038/s41586-019-1799-6>

²¹ Liu, J. A et al (2022). Artificial Intelligence (AI) for Lung Nodules: From the AJR Special Series on AI Applications. *AJR. American journal of roentgenology*, 10.2214/AJR.22.27487. Advance online publication. <https://doi.org/10.2214/AJR.22.27487>

²² Yan, T. et al (2021). Deep learning for diagnosis of precancerous lesions in upper gastrointestinal endoscopy: A review. *World journal of gastroenterology*, 27(20), 2531–2544. <https://doi.org/10.3748/wjg.v27.i20.2531>

²³ Baxi, V. et al (2022). Digital pathology and artificial intelligence in translational medicine and clinical practice. *Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc*, 35(1), 23–32. <https://doi.org/10.1038/s41379-021-00919-2>

Supporting treatment – AlaMD may provide support to clinicians throughout the treatment process and to individuals managing chronic conditions. Examples include dose estimations, such as CamDiab’s CamAPS FX software which supports the self-management of diabetes through continuous monitoring of blood glucose levels to provide optimal insulin delivery directly to the patient.²⁴ AI can also be used to reduce clinician time in preparing for radiotherapy treatments by automating the process of ‘image segmentation’ which normally sees clinicians spend large amounts of time marking up images.²⁵

Why AlaMD and why now?

The NHS – like most health systems around the world – is facing the challenge of an increasing mismatch between demand and capacity. Escalating demand is fuelled by many factors including an ageing population, a rising prevalence of multiple long-term conditions (such as diabetes and obesity) and increasing expectations as to what quality healthcare looks like. At the same time there is an increasing shortage of skilled staff across a number of core, high volume services such as radiology or pathology. In response, there has been much attention on the possibility of finding technological solutions. The ideal scenario that AlaMD might be able to provide super-human performance, free of human error and inconsistency, and scalable at will to provide expert-level care across health systems is highly attractive and is driving a strong ‘pull’ from health systems (and their funders).

This is a critical moment for the regulation of AlaMD. First, these technologies are now coming to market, and are being used within the NHS and in many health systems across the world. Second, there is a desire to rapidly increase their usage within the NHS, with extension into high volume services like screening. Third, there is growing consensus in the UK and across the world that existing SaMD regulation is not adequate for AlaMD, and may neither adequately support patient safety nor provide what innovators need. Fourth, in the post-Brexit era, regulatory approval in the UK provides access to a much smaller market than previously; the UK therefore must demonstrate to manufacturers why it is both a valuable market in its own right and an attractive location for innovation and for gathering evidence through clinical studies and post-market evaluation. Fifth, the UK has an exceptional opportunity to be a world-leader in AlaMD, combining the strengths of: a whole-population national health service committed to digital transformation; a highly-skilled medical device and health technology sector; an internationally-regarded regulator with strong expertise in medical devices including AlaMD; a strong academic sector with expertise in the evaluation of AI health technologies; and an innovative health data landscape that is creating mechanisms for safely sharing data whilst protecting privacy.

²⁴ Ware, J. et al (2022). Cambridge hybrid closed-loop algorithm in children and adolescents with type 1 diabetes: a multicentre 6-month randomised controlled trial. *The Lancet. Digital health*, 4(4), e245–e255. [https://doi.org/10.1016/S2589-7500\(22\)00020-6](https://doi.org/10.1016/S2589-7500(22)00020-6)

²⁵ Harrison, K. et al (2022). Machine Learning for Auto-Segmentation in Radiotherapy Planning. *Clinical oncology (Royal College of Radiologists (Great Britain))*, 34(2), 74–88. <https://doi.org/10.1016/j.clon.2021.12.003>

This opportunity is matched by a strong political ambition to create a regulatory system that enables AlaMD to flourish, as evidenced by the creation of the £250m NHS AI Lab.²⁶ A key driver of this ambition is the need to build a stronger, more resilient health system following the pandemic and given the regulatory freedoms granted by the UK's EU exit. The Taskforce on Innovation, Growth and Regulatory Reform identified AlaMD as one of its priority areas as part of its independent report.²⁷ It is also important to recognise the wider context of the Government's ambition for AI regulation in the UK, with a White Paper on governance and regulation expected in 2022 following the 2021 national AI Strategy.²⁸

Opportunity for improving healthcare and relieving pressure on the NHS

As outlined in Box 1, AlaMD may be used across many applications including triage, screening, diagnosis, prognosis and digital therapeutics. It is not limited to any particular set of health conditions; however, it has found most application in those healthcare pathways that depend on images (radiology, ophthalmology, digital pathology) or standard data collection (emergency medicine, critical care).

The benefits that AlaMD may bring include:

- **Efficient use of human resources:** Automation of routine, high volume tasks either replacing or supporting health professionals in those roles, releasing those health professionals to do more skilled tasks;
- **Performance:** Greater speed, accuracy and safety compared to health care professionals for appropriately selected tasks;
- **Flexibility:** Ability to scale up according to need and maintain the service 24-7;
- **Convenience:** Patients are likely to be able to undertake investigations in their own time and closer to home, supported by AlaMD review;
- **Accessibility:** Spread of expert-level diagnostic performance, where patients in under-served areas receive the same quality as those in leading institutions;
- **Addressing service gaps:** Ability to undertake tasks for which it is not possible to adequately recruit human health professionals;
- **Cost benefits:** It is likely that in the longer run AlaMD could be cost-saving to the NHS across selected applications (especially high volume, standardised tasks such as screening).

²⁶ <https://www.gov.uk/government/news/health-secretary-announces-250-million-investment-in-artificial-intelligence>

²⁷ <https://www.gov.uk/government/publications/taskforce-on-innovation-growth-and-regulatory-reform-independent-report>

²⁸ <https://www.gov.uk/government/publications/national-ai-strategy>

Opportunity for innovation and UK wealth creation

The global market for AI health technologies is expected to expand at a compound annual growth rate of 38.4% from 2022 to 2030 to reach USD 208.2 billion by 2030.²⁹ The UK is well-placed to be a leading player in this growing sector with its strengths in AI across academia, SME and industry and a national health and care system that is not only a significant market but which can evaluate these tools at scale, so providing evidence to companies that can support them as they seek new markets or applications (Table 1).

However, there is a risk of losing ground here: having left the EU, regulatory approval in the UK (as represented by the UKCA mark) provides access to a much smaller market than previously, and there is currently a risk that UK and non-UK manufacturers will disinvest in the UK. Building an efficient, responsive regulatory system that is non-burdensome and provides earlier access to market than equivalent systems elsewhere in the world, would make the UK a very attractive market, and a global hub of innovation in AIaMD. It is anticipated that in all jurisdictions, there will be increasing requirements for manufacturers of AIaMD to show 'real world' performance data. The NHS is well placed to safely provide these kinds of evaluations, and to gather data during the early post-market phase. The relative similarity of the UK population to a number of other high value markets, is particularly important in the context of AI which is prone to 'generalise' less well than other less data-dependent technologies.

Opportunity for international leadership

Since leaving the EU, the UK has an opportunity to be recognised as a leader in its own right. In the context of medical devices, a very important step has been its appointment in 2022 to be a full member of the International Medical Device Regulators Forum (IMDRF) and Medical Device Single Audit Program (MDSAP).³⁰ Within the field of AIaMD, another important step has been the increasing international collaboration. For example, MHRA has recently partnered with the FDA and Health Canada to produce the influential *Good Machine Learning Practice for Medical Device Development: Guiding Principles* (GMLP) statement.³¹ These steps highlight the opportunity that the UK has to be an international leader in this area and have global influence on the important and rapidly growing field of AI health technologies.

Table 1. UK status as a site for innovation of AIaMD: strengths and weaknesses

²⁹ [https://www.researchandmarkets.com/reports/5351653/artificial-intelligence-in-healthcare-market?utm_source=BW&utm_medium=PressRelease&utm_code=q5tlj6&utm_campaign=1728628+-+Global+Artificial+Intelligence+in+Healthcare+Market+\(2022+to+2030\)+-+Size%2c+Share+and+Trends+Analysis+Report&utm_exec=jamu273prd](https://www.researchandmarkets.com/reports/5351653/artificial-intelligence-in-healthcare-market?utm_source=BW&utm_medium=PressRelease&utm_code=q5tlj6&utm_campaign=1728628+-+Global+Artificial+Intelligence+in+Healthcare+Market+(2022+to+2030)+-+Size%2c+Share+and+Trends+Analysis+Report&utm_exec=jamu273prd)

³⁰ <https://www.gov.uk/government/news/mhra-joins-international-partnerships-to-set-global-standards-for-medicines-and-medical-devices-regulation--2>

³¹ <https://www.gov.uk/government/publications/good-machine-learning-practice-for-medical-device-development-guiding-principles>

Strengths	Potential Strengths	Relative Weaknesses
<p>Population – relatively representative of other high value markets (e.g., USA, Europe)</p> <p>National Health Service – information sharing, and coherence of strategy can support widescale adoption</p> <p>National screening services – can support efficient, widescale adoption</p> <p>MHRA – respected regulator, including in medical devices</p> <p>Industry/SME sector – significant medical device sector with rapidly growing AI health technology component</p> <p>Academic sector – expertise in AlaMD from model architecture to AlaMD evaluation</p>	<p>Multi-agency approach – commitment to work across agencies, but needs resourcing and action</p> <p>Data sharing – potential to share anonymised data efficiently to support both patient safety and innovation, but needs clarity from the ICO</p> <p>Sovereign regulator – can optimise the AlaMD regulatory framework to balance the needs of the UK, whilst also maintaining necessary international alignment</p>	<p>Small market - relative to other leading economies e.g., EU and USA</p> <p>Health service pressure - AlaMD may require significant service redesign for which health professionals and health managers may not currently have capacity</p> <p>Significant gap between demand for AlaMD regulatory review and Approved Body capacity, delaying time to market</p>

Current regulatory landscape for AlaMD

The regulation of medical devices in the UK is in a transition phase. Currently medical devices on the UK market (including SaMD and AlaMD) are regulated under the UK's *Medical Devices Regulations 2002* (as amended).³² These regulations transposed three European Union (EU) medical devices Directives (the Medical Devices Directive (93/42/EEC)³³, Active Implantable Medical Devices Directive (90/385/EEC)³⁴ and in vitro Diagnostic Medical Devices Directive (98/79/EC)³⁵ into UK law.

The Medicines and Medical Devices Act 2021³⁶ introduced powers to amend and supplement the UK medical devices regulations, heralding a UK sovereign regulatory regime. The laying of secondary legislation using these powers was due to occur on 1st July 2023. However, a 12-month extension to the standstill period was recently announced as well as acceptance of CE marked

³² <https://www.legislation.gov.uk/ukxi/2002/618/contents/made>

³³ Council Directive 93/42/EEC <https://www.legislation.gov.uk/eudr/1993/42/contents>

³⁴ Council Directive 90/385/EEC <https://www.legislation.gov.uk/eudr/1990/385/adopted>

³⁵ Council Directive 98/79/EC <https://www.legislation.gov.uk/eudr/1990/385/adopted>

³⁶ Medicines and Medical Devices Act 2021 <https://www.legislation.gov.uk/ukpga/2021/3/contents>

devices under the previous Directives for an additional three years and an additional five years if under the newer EU Regulations.³⁷ Nevertheless, the Medicines and Healthcare products Regulatory Agency (MHRA) published the Government response to the consultation on the future regulation of medical devices in the United Kingdom in June 2022 which sets out the policy direction for these legislative changes.

It is worth noting that, in parallel, the EU has been going through its own transition, moving from the Directives to the Medical Devices Regulation (2017/745) (EU MDR)³⁸ and the In vitro Diagnostic Medical Devices Regulation (2017/746) (EU IVDR).³⁹ Under the current approach to the Northern Ireland Protocol⁴⁰, Northern Ireland follows certain EU rules, with the EU MDR having taken effect from 26 May 2021 and the EU IVDR from 26 May 2022.

The MHRA is responsible for regulating the UK medical devices market. However, the MHRA do not directly assess the device, but rather depend on either self-certification by the manufacturer (for lowest risk class I devices) or on the conformity assessment undertaken by an Approved Body (AB; for all other devices). Device manufacturers of AIaMD may also need to work with other regulators, depending on the nature of their device.⁴¹

In September 2021, the MHRA announced a Software and AI as a Medical Device Change Programme which is currently ongoing. This promises to 'deliver bold change to provide a regulatory framework that provides a high degree of protection for patients and public, but also make sure that the UK is the home of responsible innovation for medical device software'.⁴² This programme comprises two workstreams: the first stream considers key reforms across the Software as a Medical Device (SaMD) lifecycle; the second considers the further challenges that AI can pose to medical device regulation. Further details on activities underpinning each work package were later published in the roadmap.⁴³ The entire programme is highly relevant to this report and full list of work-packages and their objectives are listed in [Annex C](#).

³⁷ <https://www.gov.uk/government/publications/implementation-of-the-future-regulation-of-medical-devices-and-extension-of-standstill-period/implementation-of-the-future-regulations>

³⁸ Regulation (EU) 2017/745 of the European Parliament and of the Council
<https://www.legislation.gov.uk/eur/2017/745/contents>

³⁹ Regulation (EU) 2017/746 of the European Parliament and of the Council
<https://www.legislation.gov.uk/eur/2017/746/contents>

⁴⁰ Protocol on Ireland/Northern Ireland
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/840230/Revised_Protocol_to_the_Withdrawal_Agreement.pdf

⁴¹ Reform 2019: Data-driven healthcare: regulation and regulators. Available at:
<https://reform.uk/publications/data-driven-healthcare-regulation-regulators/>

⁴² <https://www.gov.uk/government/publications/software-and-ai-as-a-medical-device-change-programme>

⁴³ <https://www.gov.uk/government/publications/software-and-ai-as-a-medical-device-change-programme/software-and-ai-as-a-medical-device-change-programme-roadmap>

The challenges

There are several regulatory challenges regarding the use of AIaMD that will be discussed throughout this report. These can be broadly grouped into challenges common to medical devices generally; challenges relating to SaMD; and challenges characteristic of AIaMD.

Challenges common to medical devices

These include issues of regulatory capacity in the face of increasing demand and complexity, and differences between international regulatory systems and health systems that can be a barrier to trade and usage.

Challenges relating to SaMD as a subset of medical devices

These include cybersecurity and data privacy risks, tracking usage, evaluating safety in the post market phase, and the need to manage frequent updates in a way that is both efficient and safe.

Challenges that are characteristic of AIaMD

These include AI bias and differential performance across people groups leading to the perpetuation or worsening of health inequalities; failure of generalisability in which the AIaMD performs poorly when deployed in a new setting or population that differs from its original training context; the impending arrival of algorithms that will continuously update in response to new data, providing an opportunity for continuous improvement but the risk of continuously evolving further away from the algorithm for which regulatory approval was given; and finally the issue of interpretability and the extent to which the user can understand how the algorithm reached its output and challenge any decision arising from that output.

Cross-cutting challenge of device equity and AIaMD

A cross-cutting challenge is the issue of device equity and the need to ensure that AIaMD that are on the UK market are not only effective and safe, but that they work for everybody. AIaMD are particularly vulnerable to differential performance across groups, although some of these issues also apply to medical devices more generally and this is the subject of a concurrent independent review on Equity in Medical Devices, Chaired by Prof. Dame Margaret Whitehead.⁴⁴ In the context of AIaMD, bias may be introduced at multiple stages including problem selection, data collection, outcome definition, algorithm development, and post deployment considerations.⁴⁵ Of particular concern is the issue of the data on which the AIaMD is trained and tested. The performance of an AIaMD in groups who are under-represented in the training and test datasets – likely to be minority groups – is likely to be worse (lack of training data) and will be less certain (lack of test data). It should be noted that both *actual* worse performance and *potential* worse performance (i.e., reduced certainty) can cause harm. This under-representation within datasets has been described

⁴⁴ <https://www.gov.uk/government/groups/equity-in-medical-devices-independent-review>

⁴⁵ Chen, I.Y. et al (2021) Ethical Machine Learning in Healthcare. *Annu Rev Biomed Data Sci.* Jul;4:123-144. doi: 10.1146/annurev-biodatasci-092820-114757.

as ‘health data poverty’, namely an “inability for individuals, groups, or populations to benefit from a discovery or innovation due to insufficient data that are adequately representative of them”.⁴⁶

However, even when datasets are appropriately inclusive and diverse, there is a risk that the data itself encodes bias. We need to consider: Why was the dataset created? Who collected the data and in what setting? Who decided what was included and what was excluded? Who made the measurements, observations and labels and how were these done?⁴⁷ Any consideration of equity in AlaMD also needs to include serious consideration of the data foundation on which such devices are trained and tested.

Cross-cutting challenge of a fast-moving sector

Lastly, it should be noted that the AlaMD sector is an area of rapid innovation, which creates a wider challenge for the regulatory system to remain agile and responsive to new developments in the technologies whilst maintaining the highest levels of patient safety.

Scope and approach

The area of AI in health was identified both in the RHC’s original horizon scanning exercises in 2020,⁴⁸ and recurrently through the stakeholder engagement exercises conducted as part of the 2021 RHC report into Medical Devices.⁴⁹ Consultation with relevant stakeholders was then conducted to define the scope and review questions with a view to ensuring that any review addressed areas of AI health technologies where regulatory reform could be most beneficial. This process led to the following overarching review question:

Review question: How can regulation of AlaMD in the UK be optimised to support the UK in being a leader in innovation and utilisation of effective, safe and equitable artificial intelligence in healthcare?⁵⁰

This question was addressed through undertaking a gap analysis of the UK’s regulatory system for AlaMD, exploring the gap between the current state and two future states (‘minimum viable product’ vs ‘world-leading system’).⁵¹ In a series of interviews and workshops, stakeholders were

⁴⁶ Ibrahim, H. et al (2021) Health data poverty: an assailable barrier to equitable digital health care. The Lancet Digital Health3, e260–e265

⁴⁷ Gebu, T et al.(2021) Datasheets for Datasets. Communications of the ACM, December 2021, Vol. 64 No. 12, Pages 86-92.

⁴⁸https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949318/potential-priority-areas-for-the-council.pdf

⁴⁹ <https://www.gov.uk/government/publications/regulatory-horizons-council-report-on-medical-devices-regulation>

⁵⁰ There are widespread views on the meaning of equity and fairness in healthcare. In the context of this report, we take a view of equity as ensuring that an individual’s characteristics, including race, gender, age, or other factors / attributes do not prevent or affect their ability to receive high quality healthcare from AlaMD.

⁵¹ ‘Minimum viable product’ in this case was defined as a regulatory system that has the necessary provisions in place to ensure safety, effectiveness and equity of AlaMD. Participants were then asked

asked to describe their current assessment of the gaps in the UK system as currently experienced, and then explore what would need to be addressed to achieve either a 'minimum viable product' or a 'world-leading system' for AIaMD regulation in the UK. Interview questions are provided in [Annex D](#).

This core work was supplemented by (1) a review of the cross-government landscape for workstreams relevant to AIaMD, and (2) a review of international comparators (desk-based and interviews with leading regulators).

what additional measures would be needed to give the UK a competitive advantage globally, described as their 'world leading' system.

3. Where are the gaps in the regulatory system?

Research conducted as part of this review identified broad consensus across stakeholder groups regarding the strengths and the weaknesses of the existing regulatory framework. The gap analysis identified wide-ranging concerns, which again were broadly consistent, but with some nuances according to the stakeholder group represented. Having identified the gaps, stakeholders were encouraged to identify potential solutions including: 1) those that were already 'in progress', 2) those that could be adapted from other international regulators, 3) those that could be adapted from other sectors and 4) those that were original.

Summary of gap analysis findings

Table 2: Issues identified across the gap analysis aligned to measures that may help address those gaps, both (1) relevant external work or (2) new recommendations arising within this report.

Issues	Other relevant work: (not exhaustive)	Recommendation from this report:
Crosscutting considerations when structuring the regulatory framework for AIaMD		
There is not a gap for another distinct regulator to fill, but the MHRA requires resourcing if it is to create and service an adequate regulatory regimen in this area that can support innovation and patient safety.	RHC Medical Devices	1
The legislative regulations are largely fit for purpose, but there is a lack of appropriate standards and guidance to apply these effectively to AIaMD. There is a need to avoid AI exceptionalism, but rather AIaMD should continue to be regulated within the broader	MHRA SaMD/AIaMD Change Programme (in progress) International standards programmes (in progress)	3

framework for SaMD (and as part of medical devices).	BS30440 (in progress)	
The emphasis of any regulatory system for AIaMD should be patient safety	IMMDS Review MHRA Patient Involvement Strategy RHC Medical Devices	12, 13
Regulatory capacity and capability		
Need for MHRA to be better resourced, and for medical devices to have a longer-term settlement Concern that MHRA is focusing more on medicines at the expense of devices Concern that MHRA is focused almost entirely on the logistics of the transition to the UKCA mark and is not adequately addressing new challenges such as AIaMD	RHC Medical Devices	1
Creating a regulatory framework that ensures that AIaMD are safe, effective and equitable		
Need for regulations to distinguish between different types of devices and their risk profiles Need to strengthen the evidence requirements for these	MHRA SaMD/AIaMD Change Programme (in progress) RHC Medical Devices	4-10

<p>technologies in both premarket and post-market phases</p> <p>Need to improve access to anonymised NHS datasets to provide additional evidence of safety prior to deployment</p> <p>Need to demonstrate that the product works in ‘the real world’</p> <p>Need to have the option of early deployment whilst evidence is still being gathered</p> <p>Concern that human factors (and potential negative impact that this may have on performance) are not adequately considered</p> <p>Need to strengthen NHS data infrastructure for more efficient and reliable ways to collect data in the post-market phase</p> <p>Need to strengthen post-market surveillance including reporting of AI errors and adverse events</p> <p>Need to make it easier for patients and public to report errors and adverse events</p> <p>Need for a less linear and more iterative approach to AIaMD development and evidence gathering</p> <p>Need for sufficient interpretability of the AIaMD to understand and interrogate its decisions (including errors)</p> <p>Need to provide a regulatory mechanism that supports</p>	<p>Algorithmic impact assessment</p> <p>Medical algorithmic audit</p> <p>EQUATOR guidelines</p> <p>Datasheets for Datasets</p> <p>Model cards</p> <p>Goldacre Review - Better, broader, safer: using health data for research and analysis</p> <p>Wade-Gery Review - Putting data, digital and tech at the heart of transforming the NHS</p> <p>Yellow Card System expansion to AIaMD (in progress)</p>	
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<p>AIaMD that are updated frequently or continuously</p> <p>Need to standardise the evaluation and reporting of performance and safety</p> <p>Concern over the potential burden of new requirements such as the pilot Algorithmic Impact Assessment</p> <p>Concerns over the possibility of adversarial attacks</p>		
Clarity of regulations for developers		
<p>Need for common definitions and understanding of terms</p> <p>Concern that new entrants to the market do not understand the existing regulations</p>	The Multi-Agency Advisory Service	11
Transparency and public trust		
<p>Concern over recent medical device controversies and lack of public trust</p> <p>Need to show not just good intent but actual progress in the regulation of AIaMD</p> <p>Lack of user engagement (professionals, patients, public) by innovators/ manufacturers</p> <p>Lack of trust in AI health technologies amongst some health staff</p> <p>Need for a publicly facing AIaMD database</p>	<p>IMMDS Review</p> <p>RHC Medical Devices</p> <p>Datasheets for Datasets</p> <p>Model cards</p> <p>Health Foundation Report: Switched on</p> <p>BEIS Public Attitudes Tracker: Artificial Intelligence, Autumn 2021, UK</p>	12, 13

<p>Need for greater transparency in how regulatory decisions are made</p> <p>Opportunity for regulatory assessments by the UK to be 'reused' by other countries as part of Good Reliance Practice, if these were more transparent</p>	<p>CDEI Public Attitudes to Data and AI</p>	
<p>National integration</p>		
<p>Need for a coherent end-to-end regulatory pathway that is clearly and consistently presented ('single source of truth')</p> <p>Need for the ICO to be included in cross-agency discussions, to ensure that data governance issues are anticipated and addressed</p> <p>Concern that any new 'horizontal' sector-neutral regulation of AI should not compromise or confuse the functional regulation of AIaMD within its 'vertical' sector of SaMD/medical devices</p>	<p>Multi-Agency Advisory Service</p> <p>NICE Evidence Standards Framework</p> <p>Office for AI White Paper on AI regulation (in progress)</p>	<p>9, 11</p>
<p>International harmonisation</p>		
<p>Concern over loss of competitiveness due to regulatory isolationism</p> <p>Need for international harmonisation</p> <p>Need for the UK to align as far as possible to one or more of the major markets</p> <p>Concern that some international approaches such as</p>	<p>Good Machine Learning Principles guidance</p> <p>IMDRF Artificial Intelligence Working Group</p> <p>International standards programmes (in progress)</p>	<p>14, 15</p>

<p>'substantial equivalence' routes are not safe in the context of AlaMD and should not be adopted or recognised by the UK</p> <p>Concern that the 1/7/2023 deadline does not provide enough time for existing devices to achieve the UKCA market</p>	<p>ITU-WHO Focus Group on Artificial Intelligence for Health (in progress)</p>	
<p>AI Bias</p>		
<p>Need to communicate clearly what is meant by 'AI bias' in this context</p> <p>Need to recognise the difference between a product that is 'safe' in all groups (ie reaches a minimum threshold of safety and performance) vs a product that is 'fair' in all groups (ie performs equally); suggestion that the former may sit primarily with MHRA, and the latter primarily with NICE or other gate-keepers</p> <p>Tension around ensuring that marginalised groups are adequately represented within datasets when those groups may have a lack of trust in authorities and specific concern as to how their data will be used</p>	<p>NIST AI Bias Report</p> <p>ISO/IEC AWI TS 12791</p> <p>NHS AI Ethics Initiative</p> <p>STANDING Together</p> <p>Medical algorithmic audit</p> <p>IGHI report</p> <p>WHO guidance</p> <p>Whitehead Review – Equity in Medical Devices</p>	<p>4, 8</p>
<p>Other</p>		
<p>Concerns that mental and physical health are being treated differently, and that there is under-regulation of various health and well-being apps that are not being registered/regulated as AlaMD</p>	<p>MHRA/NICE Project on the Regulation of Mental Health Tools</p>	

Recognition that safe, proportionate regulation should be seen as an enabler to innovation and not as a blocker	Ada Lovelace Regulate to Innovate RHC Closing the Gap	3, 6-9
Need for investment in research including regulatory science to help tackle unanswered questions in the evaluation and regulation of AIaMD	RHC Medical Devices	2, 9
<p>Footnotes: Algorithmic impact assessment: Ada Lovelace Institute/NHS Algorithmic Impact Assessment⁵²; Ada Lovelace Regulate to Innovate report⁵³; BS30440: British Standard Validation framework for the use of AI within healthcare – Specification⁵⁴; CDEI Public Attitudes to Data and AI⁵⁵; Datasheets for Datasets⁵⁶; EQUATOR guidelines: International reporting guidelines for clinical studies of AI health technologies⁵⁷; Goldacre review: Better, Broader, Safer: using health data for research and analysis⁵⁸; Good Machine Learning Practice for Medical Device Development: Guiding Principles⁵⁹; Health Foundation Report: Switched on⁶⁰; IMDRF Artificial Intelligence Working Group⁶¹; IMMDS Review: Independent Medicines and Medical Devices Safety Review led by Baroness Cumberlege⁶²; IGHl report: Addressing Racial and Ethnic Inequities in Data-driven Health Technologies⁶³; ITU-WHO AI: ITU-WHO Working Groups on AI Health Technology Evaluation and Regulation⁶⁴; Multi-Agency Advisory Service⁶⁵; MHRA/NICE project on Regulation of Mental Health Tools⁶⁶; MHRA SaMD/AIaMD Programme: MHRA Software</p>		

⁵² <https://www.adalovelaceinstitute.org/report/algorithmic-impact-assessment-case-study-healthcare/>

⁵³ <https://www.adalovelaceinstitute.org/report/regulate-innovate/>

⁵⁴ BS 30440 Safe and Ethical use of AI in Healthcare – Specification <https://standardsdevelopment.bsigroup.com/projects/2021-00605#/section>

⁵⁵ <https://www.gov.uk/government/publications/public-attitudes-to-data-and-ai-tracker-survey>

⁵⁶ Gebru T et al.(2021) Datasheets for Datasets. Communications of the ACM, December 2021, Vol. 64 No. 12, Pages 86-92.

⁵⁷ <https://www.equator-network.org/reporting-guidelines/spirit-artificial-intelligence/>

⁵⁸ <https://www.gov.uk/government/publications/better-broader-safer-using-health-data-for-research-and-analysis>

⁵⁹ <https://www.gov.uk/government/publications/good-machine-learning-practice-for-medical-device-development-guiding-principles/good-machine-learning-practice-for-medical-device-development-guiding-principles>

⁶⁰ <https://www.health.org.uk/publications/reports/switched-on>

⁶¹ <https://www.imdrf.org/working-groups/artificial-intelligence-medical-devices>

⁶² <https://www.immidsreview.org.uk/>

⁶³ <https://spiral.imperial.ac.uk/handle/10044/1/94902>

⁶⁴ <https://www.itu.int/en/ITU-T/focusgroups/ai4h/Pages/default.aspx>

⁶⁵ <https://www.nice.org.uk/about/what-we-do/digital-health/multi-agency-advisory-service-for-ai-and-data-driven-technologies>

and AI as a Medical Device Change Programme⁶⁷; Medical algorithmic audit⁶⁸; MHRA Patient Involvement Strategy⁶⁹; Model cards⁷⁰; NHS AI Ethics Initiative⁷¹; NICE Evidence Standards Framework for Digital Health Technologies (including AI)⁷²; NIST AI Bias Report: National Institute of Standards and Technology - Towards a Standard for Identifying and Managing Bias in Artificial Intelligence⁷³; Office for AI White Paper on AI regulation⁷⁴; RHC Closing the Gap: getting from principles to practice for innovation friendly regulation⁷⁵; RHC Medical Devices: RHC Report on Medical Devices⁷⁶; ISO/IEC AWI TS 12791 - Information technology - Artificial intelligence - Treatment of unwanted bias in classification and regression of machine learning tasks⁷⁷; STANDING Together: STANDards for Data Diversity, Inclusivity and Generalisability⁷⁸; Wade Gery Review: Putting data, digital and tech at the heart of transforming the NHS⁷⁹; Whitehead Review: Equity in Medical Devices independent review⁸⁰; WHO Guidance: Ethics and governance of artificial intelligence for health⁸¹; Yellow Card system expansion to AlaMD⁸².

⁶⁶ <https://www.gov.uk/government/news/mental-health-funding-of-18m-welcomed-by-mhra-and-nice-to-explore-regulation-of-digital-mental-health-tools>

⁶⁷ <https://www.gov.uk/government/publications/software-and-ai-as-a-medical-device-change-programme/software-and-ai-as-a-medical-device-change-programme-roadmap>

⁶⁸ Liu, X. et al (2022). The medical algorithmic audit. *The Lancet. Digital health*, 4(5), e384–e397. [https://doi.org/10.1016/S2589-7500\(22\)00003-6](https://doi.org/10.1016/S2589-7500(22)00003-6)

⁶⁹ https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1022370/Patient_involvement_strategy.pdf

⁷⁰ Mitchell et al. (2019) Model Cards for Model Reporting. *FAT* '19: Proceedings of the Conference on Fairness, Accountability, and Transparency*, Pages 220–229 <https://doi.org/10.1145/3287560.3287596>

⁷¹ <https://transform.england.nhs.uk/ai-lab/ai-lab-programmes/ethics/>

⁷² <https://www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies>

⁷³ Schwartz, R. et al (2022), Towards a Standard for Identifying and Managing Bias in Artificial Intelligence, Special Publication (NIST SP), National Institute of Standards and Technology, Gaithersburg, MD, [online], <https://doi.org/10.6028/NIST.SP.1270>, https://tsapps.nist.gov/publication/get_pdf.cfm?pub_id=934464 (Accessed June 3, 2022)

⁷⁴ <https://www.gov.uk/government/publications/national-ai-strategy-ai-action-plan>

⁷⁵ <https://www.gov.uk/government/publications/closing-the-gap-getting-from-principles-to-practice-for-innovation-friendly-regulation>

⁷⁶ <https://www.gov.uk/government/publications/regulatory-horizons-council-report-on-medical-devices-regulation>

⁷⁷ ISO/IEC AWI TS 12791 - Information technology — Artificial intelligence — Treatment of unwanted bias in classification and regression machine learning tasks <https://www.iso.org/standard/84110.html?browse=tc>

⁷⁸ www.datadiversity.org

⁷⁹ <https://www.gov.uk/government/publications/putting-data-digital-and-tech-at-the-heart-of-transforming-the-nhs>

⁸⁰ <https://www.gov.uk/government/groups/equity-in-medical-devices-independent-review>

⁸¹ <https://www.who.int/publications/i/item/9789240029200>

⁸² <https://transform.england.nhs.uk/ai-lab/nhs-ai-lab-roadmap/>

4. Recommendations: Bridging the gaps in AlaMD regulation

The evidence gathered from RHC's stakeholder engagement and independent review was evaluated in the context of the central review question⁸³ to develop potential solutions to the gaps identified (Table 2). These potential solutions were evaluated independently by the RHC team and were further tested through cross-sector discussions including both UK and international regulators to form the final recommendations. The RHC takes responsibility for these recommendations, but also wishes to acknowledge the many stakeholders who contributed to them through this process.

The recommendations within this report are focused on AlaMD, although it is recognised that many would also be relevant to SaMD and medical devices more generally. Further discussion of the opportunities for regulatory reform to support patient safety and innovation in medical devices is contained within the RHC Report on Medical Devices. Of the 11 recommendations contained within that report, recommendations 1-9 and 11 are highly relevant to AlaMD.

In outlining the following recommendations, we have sought to allocate responsibility and ownership where appropriate. However, it is a striking feature of this area that many of these actions will require a collective approach of multiple stakeholders (including regulators, manufacturers, and patients and the public) working collaboratively and representing a shared understanding of the outcomes desired.⁸⁴ These themes are explored in more detail in the RHC's report on 'closing the gap' between regulatory principles and practices.⁸⁵

⁸³ Review question: How can regulation of AlaMD in the UK be optimised to support the UK in being a leader in innovation and utilisation of effective, safe and equitable artificial intelligence in healthcare?

⁸⁴ Outcomes Based Cooperative Regulation (OBCR) is one such model which could be explored to achieve this. An explanation can be found here: Hodges OBE, Christopher, An Introduction to Outcome Based Cooperative Regulation (OBCR) (February 1, 2022). Available at SSRN: <https://ssrn.com/abstract=4031491> or <http://dx.doi.org/10.2139/ssrn.403149> 1

⁸⁵ <https://www.gov.uk/government/publications/closing-the-gap-getting-from-principles-to-practice-for-innovation-friendly-regulation>

A: To support patient safety and accelerate innovation, there is an urgent need to increase regulatory capacity and capability in the fast-moving field of AIaMD

MHRA Capacity

The UK has an exceptional opportunity to be a leader in AIaMD from discovery to wide-scale deployment, but this will not be realised unless we can create and service a regulatory framework that can support this.

The capacity of the MHRA and the wider regulatory system to ensure the safety of UK citizens, and to support device manufacturers, is under threat. The divergence from the EU framework and the increasing diversity and complexity of devices (including AIaMD) has increased the capacity and capability required, whilst at the same time the MHRA has been significantly reduced in size and budget, and the number of ABs has fallen to a level which is far below the capacity required. Although not specific to AIaMD, this lack of capacity was a recurrent theme amongst almost all stakeholders interviewed for this report, and was discussed in more detail previously in the RHC's report on Medical Devices.⁸⁶

Since our previous report on Medical Devices in 2021, the MHRA has announced a Change Programme for SaMD/AIaMD which is ongoing.⁸⁷ The scope of this Change Programme is excellent and aligns to many of the technical areas described in this report. The Programme deals with both necessary upgrades to SaMD regulation generally, whilst also providing a far-reaching review of how AIaMD should be regulated, noting many of the distinct challenges of this sector. If this Change Programme delivers on its potential, it would provide the UK with a template for creating one of the most advanced regulatory systems for AIaMD in the world. This Change Programme should be strongly supported and prioritised within the MHRA and beyond, to accelerate and communicate its outputs, to start realigning the UK AIaMD ecosystem around this new regulatory framework and to start building the systems that can ensure its efficient delivery.

Successful delivery of this change programme also relies on the MHRA being able to attract and retain appropriate expertise. The MHRA has world-leading expertise in the regulation of medical devices, but a combination of budget reduction and restructuring has led to a loss of experienced staff in medical devices within the MHRA, and reduced representation of these staff at senior, executive level. The UK will only be able to benefit from the opportunity of AIaMD (and medical devices more generally), if it has the capability to respond knowledgeably and definitively, and the capacity to do so in a timely manner and at scale. The need to support and strengthen the MHRA in regard to AIaMD/SaMD (and medical devices more generally) should be emphasised by the DHSC when setting the strategic direction of the MHRA for example through the remit letter.

⁸⁶ <https://www.gov.uk/government/publications/regulatory-horizons-council-report-on-medical-devices-regulation>

⁸⁷ <https://www.gov.uk/government/publications/software-and-ai-as-a-medical-device-change-programme/software-and-ai-as-a-medical-device-change-programme-roadmap>

Recommendation 1: The MHRA should be specifically resourced with a long-term funding commitment to enable them to create and service a regulatory framework that is efficient, proportionate and safe, and supports the UK in being a leader in the innovation, evaluation and utilisation of AIaMD.

This could be achieved by:

- a) Providing a longer-term settlement for the MHRA to specifically resource and accelerate the essential Change Programme for SaMD/AIaMD, and then to make sure they retain and grow high calibre individuals with the unique skills and knowledge who can deliver this;
- b) Ensuring that wider Government recognises the importance of SaMD/AIaMD as a driver for UK innovation, growth and patient benefit, whilst also recognising that this will only be realised if the regulatory system is proportionate and adequately resourced; and
- c) Ensuring that the wider MHRA and DHSC strategy recognises the distinct needs of regulation of AIaMD (and medical devices more generally) and where this differs from the regulation of medicines and ensures that expertise in devices is represented at Executive level within the MHRA.

Wider regulatory capacity and capability

The lack of AIaMD regulatory experts extends to the regulatory sector as a whole (including approved bodies, external consultants and in-house regulatory leads), and there is a need to consider how this can be rapidly addressed such as through investment in training. We reassert the recommendations of the RHC Report on Medical Devices including, '*Recommendation 6: Invest in the UK as a global centre for regulatory science and the training of regulatory professionals with expertise in medical devices, including in emerging technologies*'.

In the context of AIaMD, there is a need to upskill not only the traditional regulatory workforce but all those other gate-keepers⁸⁸ and evaluators in the health system who are a necessary part of the safe deployment of these devices (discussed later). AIaMD provide unique and unfamiliar challenges to regulators and the health institutions that deploy them. In terms of the regulators, this is not just an issue for the MHRA, but also for NICE, CQC, HRA and regulators of professional groups. There is a need to ensure that all those involved in the evaluation, usage and ongoing safety monitoring of these devices have sufficient understanding of AIaMD limitations and

⁸⁸ In this context, 'Gatekeepers' is used to refer to organisations such as the MHRA, NICE, CQC, HRA and other bodies that are involved in obtaining access to market and approval to deploy AIaMD in health settings.

vulnerabilities to be able to confidently contribute to a whole system approach to AIaMD safety, including both central and local processes.

Recommendation 2: Strengthen regulatory capacity and capability in AIaMD addressing pre-market and post-market phases, through targeted training of regulators and other gate-keepers and key contributors across the total product life-cycle.

This could be achieved by:

- a) Investing in training in AIaMD, SaMD and medical devices to build capacity within the MHRA and other relevant UK regulators, ABs, regulatory consultancies, and manufacturers;
- b) Strengthening expertise in known and emerging issues within AIaMD amongst all relevant gate-keepers (MHRA, NICE, HRA, CQC, health institutions) sufficient to enable them to provide the necessary level of scrutiny of such devices and their usage within their scope of influence; and
- c) Educating and creating capacity for relevant staff groups within the NHS so that they are confidently able to play their part in the safe deployment of these devices, and recognise their critical role in assuring patient safety.

B: There is a need for the UK to create a regulatory framework that considers the whole product life-cycle to ensure that AIaMD are safe, effective and equitable

Structuring the regulatory framework for AIaMD

Development within AIaMD is fast-moving, with advances in the technology accompanied by a need to urgently create systems that can sufficiently measure (and ideally predict) performance and safety both pre-market and post-market. Legislative regulatory mechanisms are an important cornerstone, but cannot be expected to keep pace with a rapidly evolving technology. AIaMD has already been recognised to have a number of unique regulatory requirements, not covered by existing SaMD regulation.

In this context, we recommend that the UK adopts a ‘legislatively-light’ regulatory approach with a higher dependency on standards and guidance documents, and welcome the MHRA’s current approach to implement the majority of its upcoming changes to the regulations for SaMD in the form of guidance rather than legislation as noted in the Government Response to the Consultation on Medical Devices.⁸⁹ These alternative regulatory mechanisms can be updated more frequently as the technology advances and as the regulatory requirements become more evident. In terms of standards, compliance should be aligned with *international standards* (such as those from the ISO); this international approach will support harmonisation and reduce regulatory friction between territories.

In terms of guidance, the MHRA and other relevant UK regulators have an important role in providing official guidance documents which demonstrate how the existing legislative framework should be applied, and to ensure that this is coherent between the relevant regulators so as to maximise efficiency (and minimise uncertainty) for all stakeholders. Guidance documents are potentially the most responsive, fastest moving ‘soft’ regulatory mechanism, and is an urgent need for the UK given that most international standards for AI are still in development and may be several years before formal ratification.

However, it is important to note that there are some risks to this approach. Guidance documents, as interpretations of legal requirements, can be subject to dispute and the Courts are the ultimate arbiter in terms of interpreting legislation when non-statutory guidance is involved. Additionally, whilst stakeholders noted the fast pace of developments in the field and generally welcomed the idea of a more adaptable regulatory framework, there was some caution raised in ensuring that multiple guidance documents do not become duplicative, or more burdensome to interpret for industry.

Some of the concerns raised around regulation of AIaMD, arise from a lack of awareness of the regulations that already apply to these technologies. Manufacturers of such devices must already comply with regulations pertaining to medical devices generally, and SaMD specifically. This includes legal requirements, standards and guidance documents. This may be unfamiliar territory

⁸⁹ <https://www.gov.uk/government/consultations/consultation-on-the-future-regulation-of-medical-devices-in-the-united-kingdom>

to those innovators and manufacturers who are primarily technology companies rather than being an existing medical device manufacturer.

We strongly support the position that the regulation of AIaMD should not occur in a silo, but rather should sit within the regulation of SaMD, which in turn sits within the regulation of Medical Devices. ‘AI exceptionalism’ should be avoided unless there is a need to deal with a specific area of risk (or opportunity) that is distinctive to AIaMD. We welcome the Government’s stated intention to follow such an approach as outlined in Section 65 of the response to the Consultation on Medical Devices Regulation.⁹⁰

Recommendation 3: The UK should aim for an AIaMD regulatory framework that is ‘legislatively light’ and maximises the role of standards and guidance and builds on existing regulations for SaMD whilst also addressing the specific challenges of AI technologies.

Having recognised the need to consider AIaMD within the context of SaMD regulation, there are however some areas which are regularly highlighted as being specific risk-areas when considering AIaMD. These include: (1) High data-dependency leading to risk of poor generalisability where the model performs less well when moved out of its original test context); (2) Differential performance across groups and risk of ‘AI bias’ which may worsen health inequalities; (3) ‘Black box’ approaches leading to limited interpretability of underlying working and an inability to scrutinise the basis by which the model makes its decisions and to interrogate any failures; (4) Utilisation of frequently updating models (and, in the future, continuously learning models) that challenge existing methods of assurance and safety monitoring.

These areas occur at multiple stages of the product lifecycle and are of sufficient concern to merit specific recommendations as set out below. They are being actively addressed by the MHRA, as announced in their Software and AI as a Medical Device Change Programme.⁹¹ This ongoing programme considers UK SaMD regulation end-to-end from qualification, classification, and pre-market assessment through to post-market assessment, with specific focus on key AI areas such as generalisability, interpretability and model updating. The need to address these issues is also recognised in the joint Good Machine Learning Principles (GMLP), a joint publication from the MHRA, FDA and Health Canada.⁹²

When considering these wider regulatory issues that AI poses, it is also important to note the wider context of AI legislation. The Office for AI recently set out a ‘pro-innovation approach to regulating AI’, aiming to set out a series of non-statutory cross-sectoral principles with delegation of

⁹⁰ <https://www.gov.uk/government/consultations/consultation-on-the-future-regulation-of-medical-devices-in-the-united-kingdom>

⁹¹ <https://www.gov.uk/government/publications/software-and-ai-as-a-medical-device-change-programme/software-and-ai-as-a-medical-device-change-programme-roadmap>

⁹² <https://www.gov.uk/government/publications/good-machine-learning-practice-for-medical-device-development-guiding-principles>

responsibility to individual regulators to develop appropriate regulations for their sectors.⁹³ Having heard concerns from stakeholders over the potential for a cross-sector regulatory framework for AI, modelled around the current EU approach⁹⁴, the RHC welcomes the Government’s position. This position is also one which has been advocated in past work on the topic, including in the follow up paper to the House of Lords Select Committee on Artificial Intelligence report AI in the UK.^{95 96}

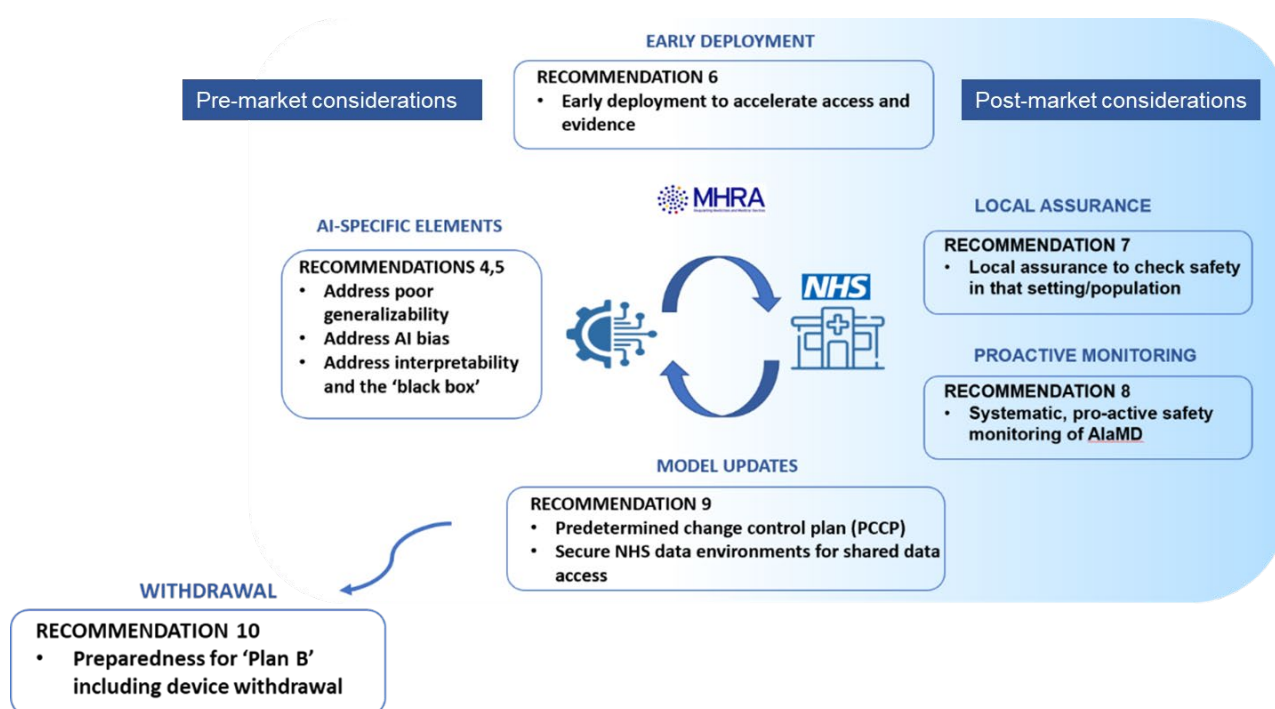


Figure 2: RHC recommendations 4-10 across phases of the product lifecycle for AIaMD.

PRE-MARKET CONSIDERATIONS

Generalisability

Most recent innovation in AIaMD is based on using an ML approach in which the model learns patterns based on the training data provided to it, such that it is able to make reliable predictions going forward. It effectively 'works out the rules' by seeing a vast number of examples of the clinical scenario. Its performance is then assessed by testing on a new dataset.

⁹³ <https://www.gov.uk/government/publications/establishing-a-pro-innovation-approach-to-regulating-ai/establishing-a-pro-innovation-approach-to-regulating-ai-policy-statement>

⁹⁴ <https://artificialintelligenceact.eu/>

⁹⁵ <https://publications.parliament.uk/pa/ld201719/ldselect/ldai/100/10002.htm>

⁹⁶ House of Lords Liaison Committee (2020) Report, AI in the UK: No room for complacency

This data-dependency of ML models and their key property of ‘working out the rules’ is both their essential strength and their core vulnerability. There is a risk that models ‘overfit’: they are so highly trained to the original dataset that they underperform when presented with new data unless it exactly aligns to the training data. This means that such models generalise poorly, since they underperform when taken out of their training environment into a real health system in which they may be exposed to populations with different characteristics or a setting which subtly alters the input data (e.g. through the use of a different model of scanner). It should be noted that some of these differences might have no effect on a human diagnostician, but lead to dangerous decline in performance of an AI system doing the same diagnostic task.

Manufacturers can increase the robustness of their AIaMD by recognising this issue and addressing it from design onwards in terms of training data (considering diversity and size of the dataset) and model features (using algorithmic approaches that reduce the tendency to over-fitting). It is recommended that this is included as evidence in their submission.

From a regulator, evaluator or user perspective, assurance of good generalisability of a model at the pre-market stage depends on being provided with evidence of its performance in external validation studies. Ideally these studies show that performance is maintained despite being exposed to: different populations representing the diversity of people that are within the intended use (e.g. different ages, sexes, or ethnic groups); different settings representing the diversity of input data that is within the intended use (e.g. different types of scanners); and over extended time-periods (providing some evidence of stability over time).⁹⁷

In addition to providing evidence of generalisability at a national level to regulators and other bodies, manufacturers should plan how, after they have regulatory approval, they will provide the evidence to local health providers that the AIaMD is likely to perform safely within their setting and when used on their local population. This is discussed further in a section on local assurance.

In considering generalisability, manufacturers should also demonstrate that care has been taken to avoid the risk of models learning artefactual associations, where they infer patterns based on incidental features that are not related to the pathology. Examples include: learning to associate the diagnosis of ‘pneumonia’ with a particular type of X-ray machine or X-ray format commonly used in ITU rather than purely based on the lung changes⁹⁸; or associating the diagnosis of ‘skin cancer’ with skin photographs of lesions which include a ruler or surgical skin markings⁹⁹. Whilst these may be true associations for those particular training datasets, they do not reflect the underlying pathology and may underperform when those artefacts are not present: for example they may fail to diagnose a patient with pneumonia when that patient has their X-ray done in an outpatient setting, or fail to diagnose a patient with skin cancer when the photograph shows no surgical skin markings.

⁹⁷ Aggarwal, R. et al (2021) Diagnostic accuracy of deep learning in medical imaging: a systematic review and meta-analysis. *npj Digit. Med.* 4, 65. <https://doi.org/10.1038/s41746-021-00438-z>

⁹⁸ Zech, J.R. et al (2018). Variable generalization performance of a deep learning model to detect pneumonia in chest radiographs: A cross-sectional study. *PLoS Med.* 2018 Nov 6;15(11):e1002683. doi: 10.1371/journal.pmed.1002683. PMID: 30399157; PMCID: PMC6219764.

⁹⁹ Winkler, J. et al (2019). Association Between Surgical Skin Markings in Dermoscopic Images and Diagnostic Performance of a Deep Learning Convolutional Neural Network for Melanoma Recognition. *JAMA dermatology*, 155(10), 1135–1141. <https://doi.org/10.1001/jamadermatol.2019.1735>

AI bias

A further issue that AI systems are particularly vulnerable to is bias. Bias in the context of AI is complex, and may arise at multiple levels.^{100 101} From a regulatory perspective, the manufacturer should as a minimum provide evidence that the AIaMD is expected to perform *safely* across the diversity of its target population as described within the intended use. AIaMD should be 'safe for all' within their intended use and not just 'safe on average'.

There is a separate argument about whether manufacturers should also demonstrate that the AIaMD performs *equally* in all groups. This is however problematic: first it may underestimate the extent to which it may be impossible to create exact equality of performance across all individuals (and thereby there will always be some groupings that demonstrate differential performance); second, it fails to distinguish differential performance that may cause harm from differential performance that may be trivial; and third, this creates a potentially unattainable bar to market entry for AIaMD such that no patient would be able to benefit from such a device since no device would come to market. We therefore recommend that differential performance *per se* is not a bar to regulatory approval, provided that it can be considered safe across these groups.

However, we recommend that manufacturers are required to show evidence of ongoing efforts to improve performance in those groups and show that they are aiming towards equity of performance. There should also be consideration of differential performance related to intersectional groups (for example performance of older women from an ethnic minority) and whether any differences are clinically important. Similarly, health technology assessors (such as NICE) and health institutions should consider whether the introduction of the AIaMD requires any additional measures in order to maximise the potential benefits for all.

Evidence: reporting of performance data pre- and post-market

There is increasing evidence that AIaMD underperform in groups who are under-represented within the training dataset, and that this may cause harm to groups who are already suffering from health disparities.^{102 103} Understanding the diversity of the dataset on which a model is trained and tested is therefore critical in anticipating how it is likely to perform in any future population.

As a minimum, manufacturers should be expected to provide the following information regarding the datasets used for training, testing and validation:

¹⁰⁰ Chen, I.Y et al (2021) Ethical Machine Learning in Healthcare. *Annu Rev Biomed Data Sci.* 2021 Jul;4:123-144. doi: 10.1146/annurev-biodatasci-092820-114757. Epub 2021 May 6. PMID: 34396058; PMCID: PMC8362902

¹⁰¹ <https://www.nist.gov/publications/towards-standard-identifying-and-managing-bias-artificial-intelligence>

¹⁰² Ibrahim, H. et al (2021) Health data poverty: an assailable barrier to equitable digital health care. *Lancet Digit Health.* 2021 Apr;3(4):e260-e265. doi: 10.1016/S2589-7500(20)30317-4. Epub 2021 Mar 4. PMID: 33678589.

¹⁰³ Wong, A. et al (2021) External Validation of a Widely Implemented Proprietary Sepsis Prediction Model in Hospitalized Patients. *JAMA Intern Med.* 2021 Aug 1;181(8):1065-1070. doi: 10.1001/jamainternmed.2021.2626. Erratum in: *JAMA Intern Med.* 2021 Aug 1;181(8):1144. PMID: 34152373; PMCID: PMC8218233

- 1) Size of the dataset and demographic profile with at least age, sex and ethnicity (subject to the scope of the intended use). The description of the dataset should also be sufficient to enable an understanding of how accurately this would reflect the population and setting into which the AIaMD would be deployed within its intended use¹⁰⁴.
- 2) Performance data should be presented on each dataset using standard methodology and nomenclature suitable for their health application,^{105,106} and with standard descriptive reporting by subgroup (to include reasonable grouping by age, sex and ethnicity). This should be presented regardless of whether the study is powered to undertake formal subgroup analysis.
- 3) Version number of the model for each set of performance data, and description of any updates to the model between those evaluations and the current AIaMD. This is essential to understand the extent to which this data provides evidence in support of the AIaMD under evaluation.

It is recognised that manufacturers may be significantly limited in the datasets that they have access to, and that these datasets may be limited in their diversity (or may not report these characteristics). These challenges were noted by some industry stakeholders consulted. In such cases, the regulator may put in place additional requirements regarding the collection and reporting of this data after deployment as part of post-market safety monitoring; this may also provide the opportunity to retrain the model to ensure good performance in under-represented groups. Mechanisms for doing this are discussed later.

Evidence: recognising labelling bias and operator bias

In addition to underperformance arising from a lack of data, bias may occur as a result of the AIaMD replicating human biases that are reflected within the data, for example clinical scores that are based on the subjective assessment of a health care professional.¹⁰⁷ This needs to be addressed across medicine (and indeed society), but within the scope of this report we recommend that, as a minimum, manufacturers provide evidence that they have considered the risk of labelling bias within the datasets they have used, and the extent to which the bias of a human operator may influence performance of the AIaMD.

Other considerations

Whilst not a key focus of this report, and covered more extensively in previous reports¹⁰⁸, it is also important to recognise the role that the UK could play in a global health context to support the safe

¹⁰⁴ <https://www.gov.uk/government/publications/software-and-ai-as-a-medical-device-change-programme/software-and-ai-as-a-medical-device-change-programme-roadmap>

¹⁰⁵ Sounderajah, V. et al (2021) Developing a reporting guideline for artificial intelligence-centred diagnostic test accuracy studies: the STARD-AI protocol *BMJ Open* 2021;11:e047709. doi: 10.1136/bmjopen-2020-047709

¹⁰⁶ Liu, X. et al (2020) Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. *Nat Med* 26, 1364–1374 (2020). <https://doi.org/10.1038/s41591-020-1034-x>

¹⁰⁷ Gumbsch, T. and Borgwardt, K., (2021) Ethnicity-based bias in clinical severity scores. *The Lancet Digital Health*, 3(4), pp.e209-e210. [https://www.thelancet.com/journals/landig/article/PIIS2589-7500\(21\)00044-3/fulltext](https://www.thelancet.com/journals/landig/article/PIIS2589-7500(21)00044-3/fulltext)

¹⁰⁸ WHO (2021): Generating Evidence for Artificial Intelligence Based Medical Devices: A Framework for Training Validation and Evaluation

deployment of AIaMD to improve health outcomes in lower- and middle-income countries (LMICs). The potential benefit of AIaMD in this context for addressing high-volume health needs including in screening is well-recognised, but direct translation of an AIaMD trained in a country such as the UK to LMICs with different demographic characteristics raises risks of poor performance and consequent harm due to a failure of generalisability¹⁰⁹. The UK has an opportunity to lead in demonstrating how local tuning of a model, local ongoing evaluation, and transparent reporting can provide the necessary assurance for countries worldwide to benefit from AIaMD including through importing such devices from other countries such as the UK.

Lastly, recognising that the issue of bias is one that is pertinent to medical devices more broadly, the RHC welcomes the Government's decision to launch an independent review on Equity in Medical Devices.¹¹⁰

Recommendation 4: Manufacturers should be required to provide evidence that they have evaluated and mitigated risks of the two major issues of (1) poor generalisability and (2) bias that can arise due to the use of AI.

This could be achieved by:

- a) Manufacturers recognising the specific risks of *poor generalisability* in AIaMD, and putting in place systematic approaches to evaluating and mitigating them;
- b) Manufacturers recognising the specific risks of *bias and selective under-performance* in AIaMD, and putting in place systematic approaches to evaluating and mitigating them;
- c) MHRA requiring this evidence to be included in the technical file provided to the AB, and available for onward sharing to relevant bodies with a patient safety remit; and
- d) Relevant downstream regulators and gatekeepers (e.g. NICE, CQC, and health institutions planning to deploy these technologies) requiring this evidence as part of their assessments.

¹⁰⁹ Burton, M. J. et al (2021). The Lancet Global Health Commission on Global Eye Health: vision beyond 2020. *The Lancet. Global health*, 9(4), e489–e551. [https://doi.org/10.1016/S2214-109X\(20\)30488-5](https://doi.org/10.1016/S2214-109X(20)30488-5)

¹¹⁰ <https://www.gov.uk/government/news/government-launches-landmark-reviews-to-tackle-health-disparities>

Interpretability

Medical interventions (e.g. drugs, devices and diagnostics) vary in the extent to which their mode of action is understood. There are many medical interventions which have proven to be safe over many years despite being relatively ‘black box’.¹¹¹ This is not a unique feature to AIaMD. However, the less well understood the mechanism of action is, the harder it is to predict its future performance (and boundaries of that performance) from mechanistic principles. An AIaMD in which the basis of the model and its outputs is well understood (‘glass box’), should in theory enable the evaluator to predict the scenarios in which the product may fail, and expect to see evidence supporting its use in these scenarios (or to see that they have been excluded by the intended use statement). A more ‘glass box’ approach also enables the evaluator to be assured that the model does not include features that would create inadvertent ‘bias by design’ which may disadvantage certain groups.

In contrast, an AIaMD in which the basis of the model and its outputs is poorly understood (‘black box’), depends almost entirely on evidence from clinical evaluation. This may be a high bar, especially where the risk class of the AIaMD is high. Essentially the evaluator will need to be assured that they have seen sufficient clinical evidence to support the AIaMD within every scenario contained within the intended use statement (for example evidence of good performance in diverse test sets and/or suitable clinical trials), or that there are mechanisms in place to ensure that underperformance in these scenarios would be recognised and mitigated to assure ongoing patient safety.

For users – healthcare professionals, patients and the public - understanding the basis of how a decision or recommendation has been made is a key contributor to trust, especially where there may be concerns about potential bias.¹¹² Even in ‘black box’ scenarios, trust may be built up over time through personal experience of good performance and supporting evidence of real-world use, however this is likely to be slower than in ‘glass box’ scenarios, where all parties can see the basis of the AIaMD output and can effectively share decision-making in response to this output.

Regardless of the nature of the underlying model, manufacturers must ensure that the outputs themselves are easily interpretable to the user without ambiguity. They must provide evidence that they have considered the extent to which human interpretation of these outputs may itself cause variation in performance and be a risk to patient safety.

We are pleased to note that the ‘human interpretability of model outputs’ features within the GMLP. There is a need however to accelerate the translation of these high-level principles into guidance to manufacturers to support them in strategic decisions (including design of the model, user interface and clinical evaluation). The MHRA have identified ‘AI interpretability’ as a work package within their SaMD/AIaMD Change Programme but need to be resourced in order to urgently create guidance in this area.

¹¹¹ Gregori-Puigjané, E. et al (2012). Identifying mechanism-of-action targets for drugs and probes. Proceedings of the National Academy of Sciences of the United States of America, 109(28), 11178–11183. <https://doi.org/10.1073/pnas.1204524109>

¹¹² Health Education England: Understanding Healthcare Workers’ confidence in AI (2022). Available at: <https://digital-transformation.hee.nhs.uk/building-a-digital-workforce/dart-ed/horizon-scanning/understanding-healthcare-workers-confidence-in-ai>

Recommendation 5: Manufacturers should provide information regarding the extent to which the basis of the outputs of the AIaMD is interpretable and can be interrogated.

This could be achieved by:

- a) Manufacturers actively seeking to maximise the extent to which an AIaMD may be interpretable, and the outputs can be interrogated;
- b) MHRA requiring this to be reported transparently in the intended use statement or other supporting documentation as part of the human-computer interaction and to support error analysis as part of safety monitoring; and
- c) Relevant downstream regulators and other gate-keepers (e.g. NICE, CQC and health institutions planning to deploy these technologies) requiring this information to support their requirements for post-market surveillance.

Accelerating innovation and early access

The traditional linear route through the regulatory pathway can be protracted if the requirements of each gate-keeping body are considered sequentially and separately (most notably MHRA and NICE). This was a recurrent issue amongst many stakeholders interviewed and noted as a particular challenge to smaller companies who may be unfamiliar with the landscape.

The recent co-operation between MHRA and NICE on the new NICE Evidence Standards Framework for Digital Healthcare Technologies (incorporating AIaMD) is a model for how these two key agencies can work synergistically, whilst recognising their critically different roles.¹¹³ This approach can enhance clarity of communication to users through harmonising language, providing clear cross-referencing to the roles of other agencies and guidance where relevant and minimising duplication.

Adopting an integrated, coherent approach across agencies and with consideration of the evidence that will be required by health institutions and users, would improve efficiency in the regulatory system and support innovators in accelerating high quality AIaMD to market. One practical step would be an agreed approach to the terms and definitions used across AIaMD, utilising international consensus wherever this is available. This approach should be supported by ongoing resourcing and increased capacity for the Multi-Agency Advisory Service (MAAS) to provide end-to-end regulatory advice for AIaMD manufacturers.¹¹⁴

¹¹³ <https://www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies>

¹¹⁴ <https://transform.england.nhs.uk/ai-lab/ai-lab-programmes/regulating-the-ai-ecosystem/the-multi-agency-advice-service-maas/>

In addition, mechanisms should be put in place that enable early, safe deployment whilst manufacturers are still gathering additional clinical and health economic evidence required by regulators and health technology assessment bodies. Positive examples include the proposed multi-agency Innovative Devices Access Pathway (IDAP) which is being piloted and the Early Deployment option in the 2022 update of the NICE Evidence Standards Framework for Digital Health Technologies.¹¹⁵ We note also that the MHRA's SaMD Change Programme contains work-packages on exploring each of *innovative access* (including IDAP) and an '*SaMD airlock rule*' in which a provisional registration may be awarded whilst further evidence is gathered.

Recommendation 6: The regulatory framework should support innovative mechanisms that enable accelerated access to market, where it is safe to do so, with more evidence generation occurring after deployment.

This could be achieved by:

- a) Developing a coherent multi-agency Innovative Devices Access Pathway for technologies that are recognised as being high-priority for the NHS and with sufficient existing safety data to support an expedited approach;
- b) Increasing resourcing and capacity for the Multi-Agency Advisory Service (MAAS) to provide end-to-end regulatory advice for AIaMD manufacturers;
- c) The MHRA providing a 'provisional registration' mechanism for appropriate technologies; and
- d) NICE recognising an 'early deployment' route within its Evidence Standards Framework for Digital Health Technologies.

¹¹⁵ <https://www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies>

POST-MARKET CONSIDERATIONS

Local assurance prior to active deployment

Concerns around the effectiveness and safety of AIaMD when deployed in 'real world' settings with potentially very different local demographics and settings were shared amongst many stakeholders consulted.

To address these risks, manufacturers should plan as to how, after they have regulatory approval, they will provide the evidence to health institutions that the AIaMD is likely to perform safely within their setting and when used for their local population. Strategies might include: 1) Showing good generalisability across previous studies that reflect diverse populations and diverse settings; 2) Comparing the extent to which those previous studies align to their local situation and may therefore be expected to predict AIaMD behaviour in their setting and population; 3) Conducting a local pre-deployment evaluation *in silico* in which the AIaMD is tested on previously collected data from the local institution (retrospective evaluation); 4) Conducting a local *silent trial* in which the AIaMD is placed within the health pathway with the intent of not influencing human decisions but rather to evaluate what the AIaMD performance would have been in that local setting if it had been acted on (prospective silent evaluation).

Health providers should recognise the importance of considering these local issues prior to deployment and assure themselves, using evidence such as described above, that they understand and have planned for any performance and safety issues of the AIaMD in their local setting and population.

Recommendation 7: Prior to a local deployment, manufacturers should work with health institutions to provide evidence that the AIaMD is likely to perform safely within their local setting, and work with them to provide that evidence where still needed.

This could be achieved by:

- a) Manufacturers working with health institutions to provide evidence of generalisability, including in external settings that resemble the local setting and population; and
- b) Manufacturers working with health institutions to assess performance and safety on previously collected data from within that setting, or undertaking a silent trial using prospectively collected data but without influencing patient care.

Proactive safety monitoring

The current reporting of performance and safety issues relating to medical devices and any medical device-associated harms is generally reactive, non-systematic and highly variable, being dependent on individuals to recognise the adverse issue and then be motivated to report it. There are concerns that it is in effect simply a ‘voluntary complaints service’. Concerns have already been raised about the inadequacy of safety reporting of medical devices both globally and within the UK.¹¹⁶ There is an additional concern relating to AIaMD since the types of errors, predictability of errors, detectability of errors and consequences of errors (including number of people affected) may all be very different to the current human systems.

To address this, the NHS, regulatory agencies (including approved bodies), manufacturers and other stakeholders need to work together to create systems that provide efficient, business-as-usual systems for monitoring performance and assuring safety of AIaMD; this should be a condition of deployment of AIaMD systems. Monitoring performance and assuring safety is an under-recognised cost which health providers, health technology assessors, and manufacturers need to allow for within their value assessments of these new technologies. Ignoring the costs of assuring safety not only leads to overly optimistic estimates of cost-effectiveness, but more concerningly means that a new technology is deployed into a health pathway that is not adequately resourced to be ‘AI ready’ in terms of safety.

Efficient ways of providing sufficient, ongoing monitoring of performance and safety for AIaMD are an area of active innovation and evaluation. A *medical algorithmic audit* approach is one example of how performance of an AIaMD may be systematically evaluated, including how errors may be interrogated and any systematic vulnerabilities identified (‘failure modes’).¹¹⁷ ¹¹⁸Both the health provider and the AIaMD manufacturer have a responsibility to ensure safety of the device and should work jointly to achieve this. Error analysis and detection of failure modes requires direct access to health data at the individual patient level.

In order to ensure the twin requirements of protecting patient privacy whilst also providing appropriate access for safety monitoring, it is recommended that health institutions utilise NHS Secure Data Environments (SDEs) in which appropriate staff from healthcare institution and the manufacturer could jointly evaluate performance, undertake error analysis, identify failure modes and respond with any corrective actions and preventive actions (CAPA). The SDE approach enables the health provider (for example an NHS Trust or an overarching NHS body) to control and monitor all access, limit the exact data fields that can be viewed, monitor and record the action of each user, and prevent accidental or deliberate egress of data. This is further discussed in Recommendation 9.

¹¹⁶ Baroness Cumberlege (2020), *Independent Medicines and Medical Devices Safety Review*: https://www.immdsreview.org.uk/downloads/IMMDSReview_Web.pdf

¹¹⁷ Liu, X. et al (2022). The medical algorithmic audit. *The Lancet. Digital health*, 4(5), e384–e397. [https://doi.org/10.1016/S2589-7500\(22\)00003-6](https://doi.org/10.1016/S2589-7500(22)00003-6)

¹¹⁸ <https://www.gov.uk/government/publications/software-and-ai-as-a-medical-device-change-programme/software-and-ai-as-a-medical-device-change-programme-roadmap>

In parallel, national reporting of AI errors and harms should be strengthened as described previously (Cumberlege Review¹¹⁹ and RHC Report on Medical Devices¹²⁰), and this should be open and transparent, including through a national registry of approved devices and associated adverse incidents (see Section C). It is worth noting that the MHRA themselves do not directly assess the device, but rather depend on either self-certification by the manufacturer (for lowest risk class I devices) or on the conformity assessment undertaken by an Approved Body (AB; for all other devices); this conformity assessment usually includes audit of the manufacturer's Quality Management System, and of varying levels of technical documentation which support the safety and performance claims of the device. The MHRA is legally entitled to request access to this information, but currently does not do so unless there are specific concerns. This 'on demand' approach means that neither the MHRA nor any other UK body provides a central data repository for critical data relating to the performance and safety of AIaMD (or indeed other medical devices). This lack of information sharing to the centre is a significant risk to patient safety, as 1) it reduces the opportunity for the MHRA to identify safety concerns or trends that may affect multiple devices, and 2) reduces the MHRA's ability to detect unsafe variations in practice by different ABs (or even within an AB), which are more likely to occur in this fast-moving field in which there is a well-recognised shortage of regulatory expertise.

Regulatory efficiency and patient safety should be further enhanced by providing mechanisms for sharing performance and safety data across relevant agencies. Traditionally, commercial considerations have been cited as a reason for not sharing information, but the emphasis here is on the performance and safety of the device, not on a detailed description of mechanism of action or other intellectual property. Furthermore, even allowing for some hesitation on the part of some manufacturers the need to support patient safety and build public trust relating to AIaMD requires a greater level of information sharing than currently exists and is part of a global trend towards openness and transparency.

In addition to being provided with the national aggregate data view of performance and safety incidents, regulators should have access to the more detailed performance and safety data at local level such as through credentialled access to the SDE.

This level of post-market surveillance represents a significant enhancement in safety monitoring which is essential if we are to enable the potential benefits of these new technologies, whilst also ensuring that deteriorations in performance can be quickly identified and acted on. It should be noted that whilst the human effort and cost of putting in these safety monitoring systems is significant, cost efficiencies would be expected once multiple technologies are being monitored in this way, since much of the system safety architecture would be shared.

There is a need to urgently explore how this can be most efficiently achieved at scale, recognising the breadth of AIaMD applications and the need to be sufficiently robust to ensure safety whilst minimising burden and cost on all parties. Consideration should be given to funding research in

¹¹⁹ Baroness Cumberlege (2020), *Independent Medicines and Medical Devices Safety Review*: https://www.immdsreview.org.uk/downloads/IMMDSReview_Web.pdf

¹²⁰ Regulatory Horizons Council (2021), *Report on Medical Devices Regulation*: <https://www.gov.uk/government/publications/regulatory-horizons-council-report-on-medical-devices-regulation>

this area, for example directly commissioned by the MHRA or via the NIHR to ensure that policy and guidance in this area takes a regulatory science approach and is evidence-based.

Recommendation 8: Key stakeholders including NHS, regulatory agencies (MHRA, CQC), and manufacturers should work together to create standards that ensure that post-market monitoring of performance and safety should be pro-active, systematic and an essential condition of deployment.

This could be achieved by:

- a) Key stakeholders – including NHS, regulatory agencies (MHRA, CQC), and manufacturers - working together to create systems that provide efficient, business-as-usual systems for monitoring performance and assuring safety of AIaMD, such as through a *medical algorithmic audit* approach including subgroup analysis and identification of ‘failure modes’;
- b) The MHRA requiring Approved Bodies (ABs) to share all performance and safety data provided to the AB regarding an AIaMD whether from pre-market conformity assessment, or through post-market follow-up or other post-market surveillance activities, and for the MHRA to hold this centrally to support their own and other relevant UK regulators’ efforts in supporting patient safety;
- c) The NHS and regulatory agencies being resourced to build multidisciplinary teams that can undertake the design, maintenance and evolution of these systems in line with an acceleration of AIaMD, and to invest in training of new types of professional (including clinician, technologist and regulator) to support this work;
- d) The Government continuing to resource and support the NHS Transformation Directorate’s Data for R&D Programme to build NHS-hosted Secure Data Environments (SDEs) that can support near-real time monitoring of safety by the relevant health institution and manufacturer working together, and to which regulators would have access as needed; and
- e) Research funding being made available to support the piloting and evaluation of these safety monitoring systems within the NHS, taking a regulatory science approach that supports evidence-based policy.

Model updates

In order to maintain and even improve AIaMD performance, it is desirable to periodically update the model through exposure to new data. Additionally, there is interest in creating AIaMD that continuously learn through a feedback loop in which the model improves as new data is provided to it. It should be noted that the need for frequent updates is common amongst SaMD and is addressed by current SaMD regulations; the concept of live updating is however a new challenge which is not addressed by these regulations.

In order to support efficiency and enable a rapid cycle of AIaMD improvement, the MHRA should support the use of predetermined change control plans (PCCP)¹²¹ in which the manufacturer can pre-specify *what* they wish to include within scope as part of their updating and *how* they would implement these changes safely. If the PCCP is accepted by the MHRA, then these updates can occur without the need for further regulatory approval, although the MHRA should be informed of these updates, a process which should be described in the PCCP.

It should be noted that the MHRA have recognised this opportunity and have identified 'AI adaptivity' as a work package within their SaMD/AIaMD Change Programme. This is a complex new programme of work, for which the MHRA need to be resourced if they are to urgently create guidance in this area, particularly regarding the use of PCCP for both frequent periodic updating and continuously learning AIaMD.

The ability to use PCCPs to maximise patient benefit from model improvements depends on creating mechanisms by which manufacturers can be provided with sufficient access to data to be able to update models in response to safety concerns or any detectable deviations in performance, whilst at the same time protecting patient privacy. At the very least this should be sufficient to enable 'mid-course correction' where a drop below a pre-specified threshold triggers a retraining of the algorithm, and where this pre-specified threshold is significantly above the level at which the AIaMD would be considered unsafe so as to prevent the need for more drastic action (such as AIaMD withdrawal). It should be noted that the MHRA Software Group is currently undertaking a programme of cross-disciplinary work on developing metrics that could signal significant changes in adaptive learning AI algorithms, which remains an area of uncertainty and requires further research.¹²²

We recommend that the SDE systems for safety monitoring (described earlier) are designed not only for *analysis* of data for safety purposes, but also enabled to use this data for *updating* of the model within the SDE to ensure that the AIaMD is optimised for use in that local population. It should be stressed that the purpose of this mechanism is for patient safety: if it is anticipated that any commercial advantage will be gained to the manufacturer through the improvement of their product as a result of updating within an NHS institution, then this should be considered within any contractual negotiations, with patient benefit as a guiding principle and with care not to compromise the value to the NHS as a whole.

¹²¹ <https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-and-Machine-Learning-Discussion-Paper.pdf>

¹²² <https://www.gov.uk/government/publications/projects-selected-for-the-regulators-pioneer-fund/projects-selected-for-the-regulators-pioneer-fund#developing-metrics-that-could-signal-significant-changes-in-adaptive-learning-ai-algorithms>

It should be noted that the 2022 Goldacre review strongly promoted the role of a subset of SDEs, Trusted Research Environments (TREs) in the context of health data research and we highlight here the equal potential value for SDEs in the context of AIaMD safety.¹²³ Investing in SDE capability across the NHS is an efficient way of supporting research for patient benefit and patient safety whilst also protecting patient privacy. Health institutions which are intending to deploy AIaMD should ensure that they have access to SDEs that are enabled to not only analyse data for safety monitoring but also, where possible, enable safe updating of the AIaMD.

Lastly, health institutions and device manufacturers need to be clear about the regulatory requirements and appropriate governance for using health data for the purposes of safety monitoring or model updating. The Information Commissioner's Office (ICO) are currently updating their 'Anonymisation, pseudonymisation and privacy enhancing technologies guidance'.¹²⁴ The expectation here is that data should be 'effectively anonymised'. Data protection law does not require the risk of identifiability to be zero, but rather that the identifiability risk is sufficiently remote. Factors that should be considered when assessing the likelihood of an individual being identified include: the data and its environment; the context, scope and purposes of the processing; technical and organisational measures applied; the motivation for de-identifying the data; the competence needed to de-identify the data; the cost and time required; and the available technologies.

¹²³ <https://www.gov.uk/government/publications/better-broader-safer-using-health-data-for-research-and-analysis>

¹²⁴ <https://ico.org.uk/about-the-ico/ico-and-stakeholder-consultations/ico-call-for-views-anonymisation-pseudonymisation-and-privacy-enhancing-technologies-guidance/>

Recommendation 9: In addition to safety monitoring, stakeholders should work together to create systems in which AIaMD performance can be optimised through model updating and innovation within a secure data environment of the NHS.

This could be achieved by:

- a) The MHRA working with key stakeholders including Approved Bodies and Manufacturers to create a PCCP mechanism that enables AIaMD to be updated to optimise performance without compromising safety;
- b) Requiring manufacturers to pre-specify the performance and safety thresholds at which their AIaMD model would require retraining, specifying these thresholds and the mechanism of retraining as part of their technical submission (and/or PCCP) to the AB;
- c) Funding further cross-disciplinary research into how to define, detect, predict and respond to significant change in performance for an AIaMD;
- d) Utilising the SDE-based safety infrastructure described earlier (Recommendation 8) to not only provide monitoring for safety purposes but to allow enable manufacturers to efficiently update models to optimise performance (and correct for any drift in performance); and
- e) The ICO providing guidance to health institutions on legal and governance issues relating to how they may provide access to anonymised, participant-level data to manufacturers and regulators for the purposes of safety monitoring and optimising performance of AIaMD.

Device withdrawal

AIaMD can show significant deterioration in performance over time, with changes that are unnoticed by a human user, triggering a change in AI performance. These can be gradual - such as due to a demographic shift in the population - or sudden - for example a software upgrade in a radiological device. There is a need to not only detect these changes early, but then to be able to respond rapidly and effectively. Prior to deployment there needs to be a pre-specified plan agreed between manufacturer and health provider to include: the thresholds of performance that necessitate action; the actions that would be required for each threshold; who is responsible for delivering on these and who is informed.

Since devices may selectively underperform in certain groups, it is important that plans for monitoring and action include analysis at the subgroup level, to identify if there are systematic safety issues for certain groups, for example by age, sex or ethnicity.

Actions that may be triggered include: modification of the device (e.g. retraining of the AI model); modification of the pathway (e.g. putting a human 'safety net' in place, whether for certain

subgroups or the whole group); withdrawal of the device. Since withdrawal of the device is a possibility, it is essential that there is a 'plan B' comprising an alternative pathway through which appropriate care can continue to be delivered in the absence of that AIaMD.

Recommendation 10: The health institution and device manufacturer should be required to agree, as part of contractual negotiations prior to deployment, an approach for monitoring and responding to performance and safety issues that adequately assures patient safety and ensures that there is a 'Plan B' in case of the need for device withdrawal.

C: There is a need to make the regulatory process for AIaMD more open and transparent, increase involvement of patients and public, and improve the clarity of communication between regulators, manufacturers and users

Clarity and availability of regulatory information regarding AIaMD for developers

Innovators and manufacturers in the AIaMD field are often relatively new to the medical device sector, being technology companies that are identifying opportunities to create AI solutions across a range of markets. These companies may fail to recognise the need to engage early with medical device regulations, and often struggle to navigate the end-to-end pathway. This may be compounded by a failure to recognise that in addition to the requirements of the MHRA as the Competent Authority for Medical Devices, there are other gate-keepers to market entry into the NHS that need to be satisfied, most notably NICE.¹²⁵

The Multi-Agency Advisory Service (MAAS; a partnership between the MHRA, NICE, CQC and the HRA focused on AIaMD)¹²⁶ provides an ideal mechanism for developing introductory ‘wayfinder’ materials that can support new entrants to the market, helping them plan and navigate their path to regulatory approval, and to understand their ongoing post-market responsibilities.

As their name suggests, MAAS would ideally provide a first contact point for manufacturers who wished to get individual advice regarding the requirements for their device, and for this advice to reflect an efficient approach to satisfying the requirements of all relevant agencies rather than only those specific to one agency. MAAS has been widely welcomed, but requires increased and longer-term funding, if it is to deliver on this important opportunity of providing a single point of advice to AIaMD manufacturers seeking to place a product on the UK market.

¹²⁵ Reform 2019: Data-driven healthcare: regulation and regulators. Available at: <https://reform.uk/publications/data-driven-healthcare-regulation-regulators/>

¹²⁶ <https://transform.england.nhs.uk/ai-lab/ai-lab-programmes/regulating-the-ai-ecosystem/the-multi-agency-advice-service-maas/>

Recommendation 11: The end-to-end regulatory pathway for AIaMD needs to be clearly communicated and supported by guidance that is accessible to innovators that are new to medical device regulation.

This could be achieved by:

- a) The key regulators and gate-keepers (MHRA, NICE, CQC, and health institutions) developing coherent approaches with a common language; and
- b) Using joint mechanisms such as the Multi-Agency Advisory Service to provide shared materials and consistent advice to users.

Public information on AIaMD regulation

The lack of information available to users and the wider public regarding the regulatory processes to approve AIaMD and regarding currently approved devices is a significant risk and needs to be urgently addressed. This should include: a publicly available register of approved devices and their key features; a publicly available adverse events/harms database; and plain English explainers describing the regulatory pathway, including pre and post-market aspects.

Regulatory guidance (such as provided by individual agencies and joint guidance from the MAAS) should include plain English explanations, so as to enable a lay audience to understand the process. The views of patients, public and even professionals regarding the use of AIaMD in routine healthcare, extends from strong enthusiasm to deep distrust. To help earn trust in this area, it is essential that the processes of pre-market and post-market evaluation are not only demonstrably robust, but also transparent and understandable.

There is an urgent need to establish a publicly available, searchable AIaMD device registry. This could be stand-alone, or part of a registry covering all SaMD or indeed all Medical Devices. Examples from other jurisdictions include the FDA's curated list of AIaMD,¹²⁷ or the EU's register for all medical devices on the EU market, EUDAMED.¹²⁸ (See also recommendations from the Cumberlege review and from the RHC Report on Medical Devices.)^{129 130}

Information for each device on this registry should at a minimum include the manufacturer's intended use statement and the risk class. This provides essential information to the users and wider public as to the exact scope for which it has been approved for use (including the setting and the intended population) and the level of risk associated. The intended use statement should be

¹²⁷ <https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices>

¹²⁸ <https://ec.europa.eu/tools/eudamed/#/screen/search-device>

¹²⁹ Baroness Cumberlege (2020), *Independent Medicines and Medical Devices Safety Review*: https://www.immndsreview.org.uk/downloads/IMMDSReview_Web.pdf

¹³⁰ <https://www.gov.uk/government/publications/regulatory-horizons-council-report-on-medical-devices-regulation>

accompanied by a plain English summary provided by the manufacturer but verified by the regulator or conformity assessment body. The risk class should be accompanied by a standardised plain English explainer.

Beyond this minimum dataset, consideration should be given to the use of ‘model cards’ which provide a standardised approach to describing the AI system, including the type of AI architecture used, the nature of the dataset used for training and testing the model, and the performance and safety data.¹³¹ These can be made more understandable through the use of nutrition-style labels.¹³² The performance and safety data included should be presented in a standardised format aligned to best international practice (Recommendation 11 of the RHC Report on Medical Devices) and should be identical to the data provided to the MHRA and other relevant regulators.

AI errors and any adverse events/harms associated with any AIaMD should be reported within a public-facing, searchable database. This could form part of an AIaMD-specific database (see previous) or form part of a wider harms database. Examples from other jurisdictions include MAUDE from the FDA¹³³ and DAEN from the TGA¹³⁴. The mechanisms for detecting these harms are discussed above (Recommendation 8).

Recommendation 12: Regulatory processes for AIaMD should have adequate explanation for public and patients to have trust in the system, which should be supported by the MHRA providing a public-facing register to include all AIaMD on the UK market, including their risk class, their intended use statement and a plain English summary of their intended use statement.

This could be achieved by:

- a) The key regulators and gate-keepers (MHRA, NICE, CQC, and health institutions) developing public explainers of regulatory guidance and documentation; and
- b) The MHRA creating a searchable public-facing register for SaMD (or AIaMD) that have been registered on the UK market, including as a minimum their risk class, their intended use statement and a plain English summary of their intended use statement.

¹³¹ Mitchell et al. (2019) Model Cards for Model Reporting. FAT* '19: Proceedings of the Conference on Fairness, Accountability, and Transparency January 2019 Pages 220–229
<https://doi.org/10.1145/3287560.3287596>

¹³² Seifert, C. et al (2019). Towards Generating Consumer Labels for Machine Learning Models. Paper presented at the 2019 IEEE First International Conference on Cognitive Machine Intelligence (CogMI).

¹³³ Manufacturer and User Facility Device Experience
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm>

¹³⁴ Database of Adverse Events Notifications <https://www.tga.gov.au/safety/safety/safety-monitoring-daen-database-adverse-event-notifications/database-adverse-event-notifications-daen>

Patient and public involvement

In our previous report on Medical Devices, our first recommendation stated that, *‘The regulation of medical devices should be centred on the needs of patients, informed by patients, record outcomes that matter to patients, and provide evaluations that are understandable to patients.’* Similarly, in the Independent Medicines and Medical Devices Safety Review, Baroness Cumberlege noted, **‘Recommendation 6: The Medicines and Healthcare products Regulatory Agency (MHRA) needs substantial revision particularly in relation to adverse event reporting and medical device regulation. It needs to ensure that it engages more with patients and their outcomes. It needs to raise awareness of its public protection roles and to ensure that patients have an integral role in its work.’**

In addition to general concerns around medical devices addressed in those reports, there is a specific risk regarding public trust in AI health technologies. Whilst many patients and members of the public are enthusiastic about the potential for AI in health, others express wide-ranging concerns including: suspicion of AI in general; a preference to have health conversations with a fellow human; anxiety around the potential loss of a human ‘in the loop’; concerns regarding ‘AI bias’; and concerns around how their data will be used and shared.¹³⁵ A survey conducted by the Centre for Data, Ethics and Innovation (CDEI) found that 59% of respondents were comfortable with the use of AI to help decide whether medical images indicate a patient has cancer and should be referred for cancer treatment, with 34% uncomfortable and 6% ‘don’t know’.¹³⁶

Manufacturers, regulators and the health sectors need to put in measures that build public trust, demonstrating the value of these technologies and the effectiveness of the pre-market and post-market systems that ensure the AIaMD being used in the UK are effective, safe and fair. A similar approach is also needed in order to build trust in the healthcare community, where there are similar wide-ranging attitudes to AIaMD, ranging from indiscriminate enthusiasm to suspicion and anxiety.¹³⁷

¹³⁵ <https://transform.england.nhs.uk/ai-lab/ai-lab-programmes/the-national-strategy-for-ai-in-health-and-social-care/surveying-public-perceptions-of-ai/>

¹³⁶ <https://www.gov.uk/government/publications/public-attitudes-to-data-and-ai-tracker-survey>

¹³⁷ Hardie, T. et al (2021) Switched on. How Do We Get the Best out of Automation and AI in Health Care? 2021. doi:10.37829/HF-2021-I03

Recommendation 13: Manufacturers, regulators and other stakeholders should demonstrate and role model greater patient and public involvement in the design, evaluation and regulation of AIaMD.

This could be achieved by:

- a) Manufacturers including patients and public in problem selection, design choices and user testing, with a particular emphasis on engaging with users of the relevant healthcare pathway; and
- b) Regulators and gate-keepers (MHRA, CQC, NICE and others) including patients and public more effectively within their decision-making processes.

D: There is an opportunity for the UK to demonstrate leadership in innovation and patient safety by pursuing international collaboration and harmonisation of the regulation of AIaMD

International leadership

The UK is an international leader in the development and evaluation of AIaMD. The MHRA is recognised for its expertise in medical device regulation and is now able to provide an independent sovereign voice on the global stage, as evidenced by taking on full membership of the IMDRF (Recommendation 5 of the RHC Medical Devices Report, 2021).¹³⁸

The MHRA's leadership in AIaMD is recognised in a number of international partnerships including the recently published Good Machine Learning Principles (GMLP), a joint output from the FDA, MHRA and Health Canada. The MHRA should be resourced to maximise its contribution to the IMDRF and other relevant international bodies that are creating international processes, standards and guidance for AIaMD. This will demonstrate the UK's leadership in this area and provides an opportunity to represent the requirements of the UK and help align the outputs and the UK's position to maximum advantage.

As noted earlier, a fast-moving field such as AIaMD is better supported by a 'legislatively-light' regulatory approach, with a higher dependency on standards and guidance documents. These alternative regulatory mechanisms can be updated more frequently as the technology advances and as the regulatory requirements become more evident. Where possible, UK requirements for demonstration of compliance should be aligned to *international* standards.

Lastly, it is worth noting again the UK's opportunity to play a leading role in a global health context in supporting LMICs to adopt AIaMD safely through adopting high standards to mitigate against AI bias and through clear and transparent reporting of regulatory decisions which may be re-used by other agencies internationally.

¹³⁸ <https://www.gov.uk/government/news/mhra-joins-international-partnerships-to-set-global-standards-for-medicines-and-medical-devices-regulation--2>

Recommendation 14: The UK should demonstrate international leadership in the regulation of AIaMD, leveraging its expertise and position to support international harmonisation in this area.

This could be achieved by:

- a) Supporting the MHRA in their new role as full member of the IMDRF programme, and resourcing them to contribute to both MDSAP and the proposed MDSRP; and
- b) Supporting and resourcing the MHRA and UK experts from across the regulatory landscape (standards bodies, industry, academia, clinical) to contribute to the development of international standards and guidance for AIaMD

Adoption of good reliance practices

Good reliance practices are an important mechanism to support regulatory efficiency. At the lower level of reliance, this would be about leveraging the work undertaken by other competent authorities, enabling manufacturers and the MHRA to avoid repeating this work, but with the MHRA retaining final, sovereign decision-making on a per product basis. At the higher level of reliance, the UK could take a unilateral recognition approach or mutual recognition approach cross medical devices; this could range from being limited to selected groups (e.g., by risk class) to being inclusive of all medical devices.¹³⁹ Either mechanism of recognition would increase efficiency. Unilateral recognition could be achieved more quickly and would significantly reduce friction on imports (enabling early access for UK patients and the NHS to these devices); mutual recognition is more complex, would be likely to take longer but would reduce friction not only to imports, but also to exports (supporting UK device manufacturers access to other markets). Recognition, whether unilateral or mutual, should only be considered with jurisdictions for which the regulatory decisions would be considered to be at least as robust as those undertaken within the UK system.¹⁴⁰ Jurisdictions and markets of highest relevance based on current imports are the European Union and the USA. See also Recommendation 7 of the RHC Report on Medical Devices.

¹³⁹ Annex 10, WHO Expert Committee on Specifications for Pharmaceutical Preparations (2021)

¹⁴⁰ These considerations should include ensuring that there is an equal emphasis on equity and mitigations put in place to avoid 'AI Bias'.

Recommendation 15: The UK should aim for regulatory efficiency in AIaMD by adopting good reliance practices (GRaIP) in medical device regulatory decision-making.

This could be achieved by:

- a) Early adoption of unilateral recognition with appropriately aligned jurisdictions (for example the USA and EU) so as to reduce friction on medical device imports, and ensure that patients within the NHS and wider UK continue to have access to the medical devices they need; and
- b) Longer-term investment in developing mutual recognition agreements with these jurisdictions to enhance exports and reduce burden on UK manufacturers.

5. Regulatory reform as a driver of innovation in AIaMD

This report on AIaMD outlines how regulatory reform can both protect patients from ineffective, unsafe and discriminatory devices whilst also supporting innovation and accelerating adoption of effective, safe and equitable devices that can support patient healthcare.

Extensive stakeholder engagement revealed a broad consensus that regulation should be understood as an enabler rather than a blocker to innovation in this space. Having clear, proportionate regulation gives industry the clarity and assurance to invest and operate in this market. In designing and evolving the regulatory framework for the AIaMD sector, regulators should seek a proportionate approach that not only protects the citizen from unsafe products but also avoids the harm to patients of inadvertently preventing beneficial products coming to market due to excessive regulatory barriers.

As highlighted throughout the report, **the introduction of safe, effective and equitable AIaMD requires a whole system, total product life cycle approach in which regulators, industry and the health system (both central and at individual provider level) work together around a common goal of patient care.** The field of AI in health is perhaps the fastest moving of all areas of health innovation: it represents a great opportunity, but also a major challenge to both the capability and capacity of our regulators and our health systems. These technologies have huge potential benefits to patients and the public, the health system and UK industry, but it is not enough to have innovative devices. We also need innovation in the regulatory framework and health systems for these devices to be safely and efficiently deployed, and to be able to respond to challenges that may arise from further developments of the technologies, such as continuously adaptive algorithms, and applications in precision medicine and direct-to-consumer products.

This report seeks to provide a realistic view of our current ‘gaps’ in the wider regulatory framework for AIaMD, but also provide a roadmap of how we can bridge these, accelerate innovation and unlock the potential of this sector. The report also recognises the very significant progress that is being made in this area, including internationally recognised leadership from the MHRA, NICE and the NHS. Leadership within the NHS is occurring both centrally (notably through the NHS-Transformation Directorate¹⁴¹) and also at local level with individual health institutions redesigning their healthcare pathways to enable them to safely adopt these technologies. A consistent thread across all stakeholder groups, is a belief that the UK has an exceptional opportunity to be a global leader in AIaMD. The UK’s existing strengths in AI research and development, medical devices, health data infrastructure, and a shared NHS were widely recognised as a powerful platform from which the UK could establish itself as the ‘go to’ place for AIaMD innovation from design to deployment, being both a significant market in its own right and with an opportunity to provide the

¹⁴¹ In 2022, NHSX and NHS Digital were merged with the NHS Transformation directorate

most efficient development and testing framework in the world. The recommendations described in this report advance this vision, improving patient safety whilst also supporting an accelerated approach to innovation that can unlock the benefits of AIaMD for patients, industry and the health system.

Annex A: Acknowledgements

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* Took part in a 1:1 or small group interview

† Provided support in reviewing a draft of the report

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- **Intellectual Property Office** – Futures Strategy Team
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- **Medicines and Healthcare products Regulatory Agency** – Johan Ordish*† and Russell Pearson*†

¹⁴² RHC membership details are here: <https://www.gov.uk/government/groups/regulatory-horizons-council-rhc#membership>

- **Microsoft Research** – Hannah Richardson*
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- **Johnson & Johnson Medical Devices**
- **Medtronic Ltd**
- **Pennine Healthcare**
- **Philips Healthcare**
- **Roche Diagnostics Ltd**
- **SGS UK Ltd**

Annex B: Snapshot of International Regulation of AIaMD

This annex sets out the international regulatory landscape for AI as a Medical Device (AIaMD).

We began by selecting jurisdictions where there are significant opportunities for the UK to learn from, based on our interviews with stakeholders, and identified the United States, Canada, Australia and Europe. We undertook a literature review, gathering information about the regulation of AIaMD in these jurisdictions. We then explored initiatives aimed at promoting international harmonisation.

United States

Who is the regulator?

The FDA (Food and Drug Administration)¹⁴³

Regulatory Approach

The FDA has developed an AI/ML-Based Software as a Medical Device Action Plan¹⁴⁴, which was published in response to feedback on their discussion paper on a proposed regulatory framework for AI in software as a medical device¹⁴⁵.

The Action Plan outlines five actions that the FDA will take:

- Develop the proposed regulatory framework further, through draft guidance on a predetermined change control plan.
- Support the development of good practices for machine learning to evaluate and improve algorithms.
- Foster an approach that is patient-centred, including device transparency for users
- Develop methods to evaluate and improve machine learning algorithms.
- Advance real-world performance monitoring pilots.

The FDA has proposed applying a total product lifecycle regulatory approach to AI as a medical device, allowing evaluation and monitoring from premarket application to post market surveillance¹⁴⁶. The approach is based on a set of principles, highlighted below:

- **Quality systems and good machine learning practices:** ensuring delivery of high-quality products that conform to standard requirements during the product lifecycle.

¹⁴³ U.S. Food and Drug Administration (FDA) <https://www.fda.gov/>

¹⁴⁴ FDA releases Artificial Intelligence/Machine Learning Action Plan <https://www.fda.gov/news-events/press-announcements/fda-releases-artificial-intelligencemachine-learning-action-plan>

¹⁴⁵ Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML) - Based Software as a Medical Device (SaMD): Discussion paper and request for feedback [discussion paper on a proposed regulatory framework for AI in software as a medical device](#)

¹⁴⁶ The SaMD regulatory landscape in the US and Europe <https://www.raps.org/news-and-articles/news-articles/2021/8/the-samd-regulatory-landscape-in-the-us-and-eu-1>

- **Initial premarket assurance of safety and effectiveness:** allowing manufacturers to submit a predetermined change control plan on a voluntary basis to the FDA. The plan anticipates two types of modification: changes in the model required when the device is already in use, and changes in a controlled manner to manage risks to patients.
- **Approach for modifications after initial review with established pre-specifications and algorithm change protocol:** If the change is within the limits of the pre-specifications and the change protocol, then the changes should only be documented in the current premarket notification. If the change leads to a new intended use, then a new premarket notification would be required for review.
- **Transparency and real-world performance monitoring:** assuring continued safety of the product for patients. Manufacturers are expected to submit updates periodically about any changes and performance metrics.

To speed up processes of approval, AI as a medical device will be assessed by the FDA or accredited third party for its design and function. Accredited Third-Party Certification¹⁴⁷ is a voluntary program in which FDA recognizes “accreditation bodies” that will have the responsibility of accrediting third-party “certification bodies.”

Depending on the risk category of the product, premarket review may be waived, and post marketing data may be considered to continue marketing of a product¹⁴⁸.

Australia

Who is the regulator?

The Therapeutic Goods Administration (TGA)¹⁴⁹ regulates medical devices in Australia, including software that meets the definition of a medical device¹⁵⁰.

Regulatory Approach

The TGA takes a risk-based approach to regulating therapeutic goods that is designed to ensure that regulation matches the risks, and the regulatory framework spans the life of medical devices, including:

- Pre-market assessment
- Market authorisation
- Post-market monitoring

The TGA has implemented reforms to the regulation of software-based medical devices, including software as a medical device, which came into effect in February 2021. Changes include clarifying the boundary of regulated software products; new risk-based classification rules; and updating the

¹⁴⁷ ASCA - Recognised Accreditation Bodies <https://www.fda.gov/medical-devices/standards-and-conformity-assessment-program/asca-recognized-accreditation-bodies>

¹⁴⁸ Accredited Third-Party Certification Program <https://www.fda.gov/food/importing-food-products-united-states/accredited-third-party-certification-program#:~:text=Accredited%20Third%20Party%20Certification%20is,certifications%20of%20foreign%20food%20facilities>.

¹⁴⁹ TGA: Overview of medical devices and IVD regulation <https://www.tga.gov.au/sme-assist/medical-devices-regulation-introduction>

¹⁵⁰ How the TGA regulates software based medical devices <https://www.tga.gov.au/resource/how-tga-regulates-software-based-medical-devices>

Essential Principles in the *Therapeutic Goods (Medical Devices) Regulations 2002*¹⁵¹ to express requirements for software-based medical devices more clearly. The risk-based classification is based on the type of information that is communicated by the software and the recipient of this information. TGA has also issued guidance¹⁵² to better advise manufacturers on complying with the Government's cybersecurity practices.

It is mandatory under the Therapeutic Goods Act 1989¹⁵³ for sponsors and manufacturers to report serious or potentially serious adverse events associated with their medical device to the TGA. TGA has a public-facing Database of Adverse Events Notifications (DAEN)¹⁵⁴, where they receive adverse event reports associated with medical devices.

Canada

Who is the regulator?

Health Canada¹⁵⁵

Regulatory Approach

Health Canada is developing a new regulatory pathway for approving medical devices with adaptive machine learning, with plans to work closely with industry and in the regulatory sandbox.

Health Canada is proposing to add a description of adaptive machine learning-enabled medical devices to Schedule G of the Food and Drugs Act¹⁵⁶, allowing these devices to be regulated as advanced therapeutic products.

This regulatory initiative was identified by Health Canada in the Health and Biosciences Sector Regulatory Review Roadmap¹⁵⁷.

Europe

Who is the regulator?

In the European Union (EU), medical devices must undergo conformity assessment to demonstrate their safety and performance. Medical devices are regulated at the EU member state level, but the European Medicines Agency (EMA) is responsible for evaluation through a

¹⁵¹ Therapeutic Goods (Medical Devices) Regulations 2002
<https://www.legislation.gov.au/Details/F2022C00693>

¹⁵² Medical Device Cyber Security Guidance for Industry <https://www.tga.gov.au/how-we-regulate/manufacturing/medical-devices/manufacture-guidance-specific-types-medical-devices/regulation-software-based-medical-devices/medical-device-cyber-security-guidance-industry>

¹⁵³ Therapeutic Goods Act 1989 <https://www.legislation.gov.au/Details/C2021C00376>

¹⁵⁴ Database of Adverse Event Notifications – Medical Devices <https://apps.tga.gov.au/prod/DEVICES/daen-entry.aspx>

¹⁵⁵ Health Canada <https://www.canada.ca/en/health-canada.html>

¹⁵⁶ Food and Drugs Act 1985 <https://laws-lois.justice.gc.ca/eng/acts/f-27/fulltext.html>

¹⁵⁷ Targeted regulatory review – Regulatory Roadmap <https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/targeted-regulatory-reviews/health-biosciences-sector-regulatory-review/roadmap.html>

centralised procedure.¹⁵⁸

Regulatory Approach

The European Commission¹⁵⁹ published an AI package in April 2021, which proposed new rules and actions focussed on trustworthy AI. The package consists of:

- A communication on fostering a European Approach to AI¹⁶⁰
- A Coordinated Plan with Member States¹⁶¹
- A proposal for AI regulation¹⁶²

Proposed European Union regulations¹⁶³ could have a global impact on medical device and diagnostic companies, with additional requirements on the use of AI (Artificial Intelligence) and large fines for noncompliance. The draft regulations classify AI systems into three risk categories: unacceptable-risk systems, high-risk systems, and limited – and minimal – risk systems, as highlighted in Table 1 below.

Table 1: The three risk categories in the European Union’s draft AI regulations (adapted from Benjamin et al 2021¹⁶⁴)

Unacceptable – risk AI systems	High-risk AI systems	Limited – and minimal – risk AI systems
<ul style="list-style-type: none"> • Subliminal, manipulative, or exploitative techniques causing harm • Real-time, remote biometric identification systems used in public spaces for law enforcement • All forms of social scoring 	<ul style="list-style-type: none"> • Systems that evaluate consumer creditworthiness • Recruiting or employee-management systems • Systems using biometric identification in non-public spaces • Safety-critical systems (e.g., systems that would put the health of citizens at risk due to failure) • Any systems used in the administration of justice 	<ul style="list-style-type: none"> • AI chatbots • AI-enabled video and computer games • Spam filters • Inventory-management systems • Customer-and-market segmentation systems • Most other AI systems

¹⁵⁸ <https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices>

¹⁵⁹ A European approach to artificial intelligence <https://digital-strategy.ec.europa.eu/en/policies/european-approach-artificial-intelligence>

¹⁶⁰ Communication on fostering a European approach to artificial intelligence <https://digital-strategy.ec.europa.eu/news-redirect/709089>

¹⁶¹ Coordinated plan on artificial intelligence 2021 review <https://digital-strategy.ec.europa.eu/news-redirect/709091>

¹⁶² Proposal for a regulation laying down harmonised rules on artificial intelligence <https://digital-strategy.ec.europa.eu/news-redirect/709090>

¹⁶⁴ What the draft European Union AI regulations mean for business <https://www.mckinsey.com/capabilities/quantumblack/our-insights/what-the-draft-european-union-ai-regulations-mean-for-business>

In the new plans, AI systems classed as “high-risk” would only be allowed on the EU (European Union) market if they comply with requirements and ensure they do not impose unacceptable risks, such as those highlighted in Table 1, and medical devices are one of the products that could be placed in this category¹⁶⁵. Requirements include:

- Implementation of a risk-management system
- Data governance and management
- Technical documentation
- Record keeping and logging
- Transparency and provision of information to users
- Human oversight
- Accuracy, robustness, and cybersecurity
- Conformity assessments: algorithmic impact assessments that analyse datasets, biases, user interaction, and overall design and monitoring outputs.
- Registration with EU member-state Government
- Post market monitoring system

Requirements for transparency apply to all risk categories, specifically the obligation to ensure users are aware of interacting with machines to enable them to make informed decisions about whether to continue their interaction and notifying users if content has been manipulated by AI to falsely represent this content.

International harmonisation

The following section highlights initiatives that aim to promote international harmonisation in the regulation of AI-MD. International harmonisation is a key theme throughout the main report and has been highlighted multiple times during interviews with stakeholders, who were keen to encourage as much harmonisation as possible with the rest of the world.

International Medical Devices Regulators Forum:

The International Medical Devices Regulators Forum (IMDRF)¹⁶⁶ is a voluntary group of medical device regulators who have come together from around the world, aiming to accelerate international regulatory harmonization and convergence for medical devices.

The Management Committee oversees Ad Hoc Working Groups¹⁶⁷ which draw upon expertise from stakeholder working groups such as industry, academia, healthcare professionals and consumer and patient groups.

The Artificial Intelligence Medical Devices Working Group¹⁶⁸ aims to achieve an aligned approach to the management of AI-based medical devices. The first project of the Working Group covers machine learning-based medical devices representing AI technology applied to medical devices

¹⁶⁵ EU plans to impose additional regulations on medtech AI products, other 'high-risk' systems <https://www.medtechdive.com/news/eu-plans-to-impose-additional-regulations-on-medtech-ai-products-other-hi/600022/>

¹⁶⁶ International Medical Device Regulators Forum <https://www.imdrf.org/>

¹⁶⁷ Working Groups <https://www.imdrf.org/working-groups>

¹⁶⁸ Artificial Intelligence Medical Devices <https://www.imdrf.org/working-groups/artificial-intelligence-medical-devices>

and further standardizes terminology for machine learning-based medical devices among member states.

The MHRA is, as of 2022, a full member of the IMDRF, having previously been an official observer. The World Health Organisation is an official observer.

Medical Device Single Audit Program (MDSAP):

In 2012, the IMDRF identified a work group to develop documents for advancing a Medical Device Single Audit Program (MDSAP)¹⁶⁹, allowing an MDSAP-recognised auditing organisation to conduct a single regulatory audit of a device manufacturer that satisfies relevant requirements of regulatory authorities taking part in the program. The TGA, Health Canada, FDA, and - as of 2022 - the MHRA are participating in the MDSAP; the EU is recognised as an official observer.¹⁷⁰

Objectives:

- To operate a single audit program that provides confidence in program outcomes.
- To enable the appropriate regulatory oversight of medical device manufacturers' quality management systems while minimizing regulatory burden on industry.
- To promote more efficient and flexible use of regulatory resources through work-sharing and mutual acceptance among regulators while respecting the sovereignty of each authority.
- To promote, in the longer term, greater alignment of regulatory approaches and technical requirements globally based on international standards and best practices.
- To promote consistency, predictability and transparency of regulatory programs by standardizing:
 - oversight practices and procedures of participating regulators over third party auditing organizations, and
 - practices and procedures of participating third party auditing organizations.
- To leverage, where appropriate, existing conformity assessment structures.

Outcome:

An international coalition of countries dedicated to pooling technology, resources, and services to improve the safety and oversight of medical devices in a more efficient manner that is also less burdensome for industry.

MDSRP:

In 2019, regulators participating in the IMDRF met in Tokyo to discuss a medical device single review program (MDSRP)¹⁷¹ that will allow for a single regulatory pre-market review to satisfy the needs of multiple regulators and was modelled after the MDSAP.

¹⁶⁹ FDA-TGA-ANVISA-HPFB Cooperation in the Medical Device Single Audit Program (MDSAP) <https://www.fda.gov/international-programs/cooperative-arrangements/fda-tga-anvisa-hpfb-cooperation-medical-device-single-audit-program-mdsap>

¹⁷⁰ Medical Device Single Audit Program (MDSAP) <https://www.fda.gov/medical-devices/cdrh-international-programs/medical-device-single-audit-program-mdsap>

¹⁷¹ IMDRF gains ground with plans for a Medical Device Single Review Program <https://www.raps.org/news-and-articles/news-articles/2019/1/imdrf-gains-ground-with-plans-for-a-medical-device>

ITU-WHO Focus Group on Artificial Intelligence for Health

The ITU/WHO Focus Group on artificial intelligence for health¹⁷² works in partnership with the World Health Organization (WHO) to establish a standardized assessment framework for the evaluation of AI-based methods for health, diagnosis, triage or treatment decisions.

US, UK, Canada: GMLP for medical devices

The US Food and Drug Administration (FDA), Health Canada, and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) have jointly identified 10 guiding principles that can inform the development of Good Machine Learning Practice (GMLP)¹⁷³. They cover the whole life cycle of devices, and the key elements of GMLP, including using appropriate datasets and carrying out sufficient testing, and set out an ongoing recommendation to manage risk¹⁷⁴.

The principles identify areas of potential collaboration for the IMDRF, international standards organisations and other bodies to advance GMLP, including research, creating educational resources, regulatory policies and guidelines, consensus standards and international harmonisation¹⁷⁵.

BSI and Association for Advancement of Medical Instrumentation (AAMI)

Together BSI and AAMI have created guidance on the application of **ISO 14971** (the application of risk management to medical devices) specifically for Artificial Intelligence (AI) and Machine Learning (ML) medical devices¹⁷⁶. The guidance covers consideration for AI/ML-based solutions in relation to the general requirements for the risk management system, risk analysis, risk evaluation, risk control and the evaluation of the overall residual risk. It focuses on the risks that are elevated or unique to AI-based medical devices¹⁷⁷.

¹⁷² Focus group on “Artificial Intelligence for Health” <https://www.itu.int/en/ITU-T/focusgroups/ai4h/Pages/default.aspx>

¹⁷³ Good Machine Learning Practice for Medical Device Development: Guiding Principles <https://www.gov.uk/government/publications/good-machine-learning-practice-for-medical-device-development-guiding-principles>

¹⁷⁴ US, UK and Canada Regulators Collaborate to Develop “10 Guiding Principles” for Good Machine Learning Practices (GMLP) for Medical Devices <https://www.covingtondigitalhealth.com/2021/10/u-s-uk-and-canada-regulators-collaborate-to-develop-10-guiding-principles-for-good-machine-learning-practices-gmlp-for-medical-devices/>

¹⁷⁵ UK, USA and Canadian regulators identify 10 guiding principles to be addressed when medical devices use AI or machine learning software <https://www.gov.uk/government/news/uk-usa-and-canadian-regulators-identify-10-guiding-principles-to-be-addressed-when-medical-devices-use-ai-or-machine-learning-software>

¹⁷⁶ Consultation on new guidelines for the application of ISO 14971 to artificial intelligence and machine learning <https://complianc navigator.bsigroup.com/en/medicaldeviceblog/consultation-on-new-guidelines-for-the-application-of-iso-14971-to-artificial-intelligence-and-machine-learning/>

¹⁷⁷ The hype about AI in healthcare: an introduction to machine learning <https://www.medtechfoundation.org/post/the-hype-about-ai-in-healthcare-an-introduction-to-machine-learning>

Annex C: MHRA Software and AI as a Medical Device Change Programme

Published 17 October 2022

Workstreams below (including their problem statements and objectives only) reproduced from: <https://www.gov.uk/government/publications/software-and-ai-as-a-medical-device-change-programme/software-and-ai-as-a-medical-device-change-programme-roadmap#work-packages>

Workstream 1

WP 1 Qualification

Problem statement: There is currently a lack of clarity as to what qualifies as SaMD and software in a medical device; this clarity is required to ensure appropriate, effective and proportionate regulation of these devices.

Objectives

- Ensure medical device regulations capture sufficient breadth of software to protect patients and public
- Ensure there is sufficient clarity yet flexibility of qualification to effectively and proportionately regulate SaMD
- To improve the wider regulation of digital health, through supporting and working with other regulators and processes where software does not qualify as a medical device

WP 2 Classification

Problem statement: Currently, the Medical Device Regulations 2002 (as amended) do not classify software proportionate to the risk it might pose to patient and public safety.

Objectives

- Ensure classification rules closely follow the risk that specific SaMD poses to patient and public safety where this is known
- Ensure classification rules impose safety and performance requirements proportionate to the risk which SaMD applications pose

- Ensure that classification rules provide sufficient flexibility so that the risk profile of novel devices can be addressed without needlessly restricting innovation.

WP 3 Premarket requirements

Problem statement: Clearer premarket requirements that fit software are needed to ensure a smoother path to market for manufacturers and better protection for patients and the public.

Objectives

- Ensure SaMD is supported by adequate data on safety, effectiveness, and quality prior to being placed on the market, ensuring these requirements are proportionate to the risk the device presents
- Ensure that premarket requirements, especially clinical evidence and clinical investigation requirements, are clear in how they apply to and are appropriate for SaMD
- Ensure that any premarket submission includes all necessary information to support the safe use of SaMD.

WP 4 Post Market

Problem statement: The safety signal for SaMD that MHRA receives needs to be stronger. The post market surveillance system needs to be adapted so that signals are received and not lost to noise. This is needed to enable stronger vigilance by manufacturers and to detect and mitigate the risk of patient safety incidents. Additionally, change management requirements also require review given the challenges seen in the software, including but not limited to rapid updating.

Objectives

- Strengthen our post market surveillance system to support quicker and more comprehensive capture of adverse incidents for SaMD, enabling better detection of safety signals,
- Consider how to utilise real world evidence to provide further assurance that SaMD functions as intended, maintains performance, and continues to provide assurance with respect to safety by supporting investigation of signals
- Articulate clear change management requirements for SaMD

WP 5 Cyber Secure Medical Devices

Problem statement: Existing medical device regulations do not currently consider the evolving state of the art for mitigating the risks presented by cyber security vulnerabilities and the operational issues presented by legacy software medical devices and systems.

Objectives

- Articulate how cybersecurity issues translate to SaMD issues
- Ensure that cybersecurity is adequately reflected in SaMD requirements and in post market surveillance requirements
- Work closely with other bodies, for instance, through the Connected Medical Device Security Steering Group to ensure SaMD cybersecurity policy capitalises on synergies

Workstream 2

WP 9 AI RIG (AI Rigour)

Problem statement: There is a lack of clarity on how to best meet medical device requirements for products utilising artificial intelligence, to ensure these products achieve the appropriate level of safety and meet their intended purpose.

Objectives

- Utilise existing regulatory frameworks to ensure AIaMD placed on the market is supported by robust assurance that it is safe and effective
- Develop supplementary guidance to better ensure AIaMD placed on the market is supported by robust assurance with respect to safety and effectiveness
- Outline technical methods to test AIaMD to ensure the device is safe and effective

WP 10 Project Glass Box (AI Interpretability)

Problem statement: Current medical device requirements do not take into account adequate consideration of human interpretability and its consequence for safety and effectiveness for AIaMD.

Objectives

- Articulate how opacity of AIaMD translates into safety, effectiveness, or quality concerns
- Develop guidance regarding interpretability of AIaMD to ensure that AI models are sufficiently transparent to be reproducible and testable
- Develop guidance regarding interpretability of AIaMD to ensure that the relationship of interpretability to usability is made plain and emphasised in relation to safety and effectiveness

WP 11 Project Ship of Theseus (AI Adaptivity)

Problem statement: Existing requirements and processes surrounding the notification and management of change need to fit and be streamlined for AIaMD.

Objectives

- Articulate problems of fit with medical device regulation for adaptive AIaMD, distinguishing between models that are locked, batch-trained, or continuous learning on streaming data
- Clarify how adaptive AIaMD of each type might fit within existing change management processes required by medical device regulations
- Where appropriate, craft new guidance for adaptive AIaMD that does not fit within existing change management processes

Annex D: Interview Questions

Exam question:

How can regulation of AIaMD in the UK be optimised to support the UK in being a leader in innovation and utilisation of effective, safe and equitable artificial intelligence in healthcare?

Both 'hard' (legislative) and 'soft' (including alternatives to legislation such as guidance and standards) regulatory measures are being considered.

1. In your opinion, are there any gaps in current regulatory framework for AIaMD, either in the system itself or how it is delivered?
2. What do you think are the essential elements that need to be put in place to make the system effective, safe and equitable?
3. What are the additional elements required to make the UK world leader in this space?
4. In your opinion, how could regulatory reform support innovation in the UK for AIaMD?
5. Are you aware of any measures currently in development within the UK that are likely to address any of these issues?
6. Are you aware or drawn to international practices that better match your vision of a fit-for-purpose or sector-leading AIaMD regulatory framework?
7. Are you aware of any practices in other sectors that could be drawn on for a fit-for-purpose or sector-leading AIaMD regulatory framework?



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