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REVIEW

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Artificial intelligence in medical device software and high-risk medical devices – a review of definitions, expert recommendations and regulatory initiatives

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ABSTRACT

Introduction: Artificial intelligence (AI) encompasses a wide range of algorithms with risks when used to support decisions about diagnosis or treatment, so professional and regulatory bodies are recommending how they should be managed.

Areas covered: AI systems may qualify as standalone medical device software (MDSW) or be embedded within a medical device. Within the European Union (EU) AI software must undergo a conformity assessment procedure to be approved as a medical device. The draft EU Regulation on AI proposes rules that will apply across industry sectors, while for devices the Medical Device Regulation also applies. In the CORE-MD project (Coordinating Research and Evidence for Medical Devices), we have surveyed definitions and summarize initiatives made by professional consensus groups, regulators, and standardization bodies.

Expert opinion: The level of clinical evidence required should be determined according to each application and to legal and methodological factors that contribute to risk, including accountability, transparency, and interpretability. EU guidance for MDSW based on international recommendations does not yet describe the clinical evidence needed for medical AI software. Regulators, notified bodies, manufacturers, clinicians and patients would all benefit from common standards for the clinical evaluation of high-risk AI applications and transparency of their evidence and performance.

1. Introduction

Artificial intelligence (AI) is an oxymoron. In their seminal proposal, John McCarthy and his colleagues suggested that a machine could be made to simulate 'every aspect of learning or any other feature of intelligence' [1], but such 'general' AI remains an elusive goal that for most medical applications may always be inappropriate. Even in non-clinical contexts the name is misleading: computers process binary code but they are not conscious organisms and they cannot understand its meaning [2]. Nonetheless, the term artificial 'intelligence' is widely applied to an extensive range of software algorithms with varying functions, sophistication and transparency, including natural language processing and machine learning (ML).

Multiple administrative, scientific, diagnostic and therapeutic applications in healthcare already depend on some variant of AI to perform a myriad of tasks. In essence, most can be considered advanced statistical methods for interpreting large datasets or performing complex analyses [3]. It seems unscientific to lump such a wide array of techniques together under a single umbrella term 'AI' and to try to find a precise definition for AI that covers all the possibilities. From clinical and regulatory perspectives, AI should not be the objective but rather always a means to an end. Irrespective of whether an analytical algorithm (AI software) constitutes a medical device in its own right or is an integral part of a medical device, it should be evaluated for regulatory approval according to the ultimate purpose claimed by its manufacturer. The level of clinical evidence and the criteria by which it will be evaluated will be determined by the clinical risks inherent in the AI application if it reaches an erroneous conclusion for the individual patient or directs an inappropriate action within the context of its use.

Despite the lack of precision and frequent nonspecificity of use of the term AI, many task forces or working groups have defined it and developed classifications as a prelude to formulating standards or regulatory guidance for clinical evaluation. An alternative framework for stratifying medical device

software (MDSW) according to the risks associated with its use was recommended by the International Medical Device Regulators Forum (IMDRF) [4] and adopted with some modifications by the EU [5]. Its approach can guide proportionate assessment of AI medical devices in the European Union (EU), determined by existing legislation but taking more account of expert scientific guidance. To contribute to the development of appropriate methodologies for clinical evaluation, we have reviewed and here summarize:

- Regulatory definitions and terms relating to AI
- Consensus recommendations from professional and academic experts
- Standards relevant to medical AI proposed by international standards organizations
- Projects by regulatory bodies to develop requirements for clinical evaluation of AI
- European laws with relevance to clinical uses of AI, and
- Transparency and interpretability of AI and ML methodologies.

This is a narrative rather than a systematic review, which summarizes the results of literature searches made using combinations of terms related to artificial intelligence, machine learning, standards, and regulations. We also searched the websites of international regulators and standards organizations, and followed up sources mentioned in reference lists and official publications. Table 1 defines some of the common terms that are used in this paper [6–11].

2. Background and the CORE-MD project

In the European Union (EU), medical devices are governed by Regulation (EU) 2017/745 on Medical Devices (MDR) which has been applicable since May 2021. Article 2(1) defines a medical device as 'Any instrument, apparatus, appliance, *software*, implant, reagent, material or other article, *intended by the manufacturer* to be used, *alone or in combination*, for human beings for one or more of the following specific medical purposes [...] *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease* [or] investigation, replacement or modification of the anatomy or of a physiological or pathological process or state' [12] (our emphases).

The term 'software' was added to the description in 2007 under the previous EU medical device directives [13], while prediction and prognosis were first included among the purposes of a medical device by the MDR. The Medical Device Coordination Group (MDCG) of the European Commission published guidance in 2019 about what should qualify as MDSW and how it should be classified [5], and in 2020 it added recommendations for clinical evaluation (of software in general) [14].

The explosion of interest in harnessing the power of AI to accelerate medical research and exploit its capacity when addressing specific clinical challenges, has produced many applications already approved by regulators without their scientific basis being transparent. In the USA in 2017–2018, for example, the Food and Drug Administration (FDA) approved 11 out of 14 AI software products through their 510(k) pathway, which means on the basis of equivalence to existing devices and without new clinical evidence [15]. Concerning 222 AI medical devices approved between 2015 and 2020, 92% had been assessed through the 510(k) pathway [16]. In another study, only 9 out of 64 AI medical devices had undergone de novo or premarket approval [17].

In Europe, peer-reviewed literature was available for only 36 of 100 AI medical device software products that were CE-marked for use in diagnostic radiology, and the published evidence addressed diagnostic accuracy rather than clinical efficacy or impact [18]. Out of 240 devices approved under the previous EU medical device directives, only 1% were considered high-risk (class III) [16]. At that time, most medical device software was considered Class I and self-certified without external review, whereas under the MDR the majority will

Table 1. Definitions.

Term	Definition recommended and/or used in this paper
Artificial Intelligence (AI)	*Preferred simple definition =* The science of making machines do things that would require intelligence if done by men. [Minsky] [6] *EU definition recommended by the High Level Expert Group =* See Table 2 for full quotation
Machine learning (ML)	A sub-discipline of AI, where systems can learn from data to solve problems without being explicitly programmed to do so.
Deep learning	A form of ML that uses 'deep' neural networks (mathematical models inspired by the architecture of the human brain).
AI model	A physical, mathematical or otherwise logical representation of a system, entity, phenomenon, process or data. [7]
Model parameter	Internal variable of a model. [7]
AI system	An engineered system that generates outputs such as content, forecasts, recommendations or decisions for a given set of human-defined objectives. [7] An AI system is composed of (1) the training, validation, and evaluation data; (2) the model structure and parameter values; and (3) the algorithms used to pre- and post-process data and to train and deploy the AI system.
Training	Process to optimize the parameters of an ML model, based on an ML algorithm, by using training data. [7]
Data	Consists of **training data** (data used to train the model), **validation data** (data used to compare the performance [and fine tune] different candidate models), and **evaluation data** (data used to assess the performance of a final model). [7]
Interpretable AI	An AI system with the ability to explain or to present [its output] in understandable terms to a human. [8] The availability of information about each component of an AI system.
Explainable AI	The availability of post-hoc aids or models to explain the decisions of an AI system. [9]
Transparency	[The ability of an AI system] to be open to appropriate public examination and oversight. [10]
Trustworthy AI	An AI system that is lawful (complying to all applicable laws and regulations), ethical (adherent to ethical principles and values), and robust (from both technical and sociable perspectives). [11]

Table 2. Definitions of artificial intelligence in reports and regulatory documents with relevance for medical devices.

Organization/institution	Document details (title, year)	Verbatim extract from definition
International Medical Device Regulators Forum (IMDRF)		
Working Group on Software as a Medical Device (SaMD)	Software as a medical device (SaMD): Key definitions. IMDRF/SaMD WG/N10: 2013 [32]	"Software as a Medical Device" (SaMD) is defined as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.
SaMD Working Group	Software as a medical device: clinical evaluation. IMDRF/SaMD WG/N41: 2017 [33]	SaMD can best be described as software that utilizes an algorithm (logic, set of rules, or model) that operates on data input (digitized content) to produce an output that is intended for medical purposes as defined by the SaMD manufacturer.
Working Group on Artificial Intelligence Medical Devices	Machine Learning-enabled Medical Devices – A subset of Artificial Intelligence-enabled Medical Devices: Key Terms and Definitions. IMDRF/AIMD WG (PD1)/N67. Proposed document, 16 September 2021. [34]	Machine Learning-enabled Medical Device (MLMD) = A medical device that uses machine learning, in part or in whole, to achieve its intended medical purpose.
European Union		
High-Level Expert Group on Artificial Intelligence	A definition of AI: main capabilities and scientific disciplines. (2018) [35]	AI refers to systems designed by humans that, given a complex goal, act in the physical or digital world by perceiving their environment, interpreting the collected structured or unstructured data, reasoning on the knowledge derived from this data and deciding the best action(s) to take (according to pre-defined parameters) to achieve the given goal. AI systems can also be designed to learn to adapt their behaviour by analysing how the environment is affected by their previous actions.
High-Level Expert Group on Artificial Intelligence	Ethics Guidelines for Trustworthy AI (2019) [11]	AI systems are software (and possibly also hardware) systems designed by humans that, given a complex goal, act in the physical or digital dimension by perceiving their environment through data acquisition, interpreting the collected structured or unstructured data, reasoning on the knowledge, or processing the information, derived from this data and deciding the best action(s) to take to achieve the given goal. AI systems can either use symbolic rules or learn a numeric model, and they can also adapt their behavior by analysing how the environment is affected by their previous actions.
Medical Device Coordination Group	MDCG 2019–11. Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR (2019). [5]	"Software" is defined as a set of instructions that processes input data and creates output data. Medical device software (MDSW) is software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a "medical device" in the Medical Devices Regulation or In Vitro Diagnostic Medical Devices Regulation.
European Commission	Proposal for a Regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence. Article 3.1, and *Annex I (2021) [37] (also known as the AI Act)	AI system means software that is developed with one or more of the techniques and approaches listed* and [that] can, for a given set of human-defined objectives, generate outputs such as content, predictions, recommendations, or decisions influencing the environments they interact with. * (a) Machine learning approaches, including supervised, unsupervised and reinforcement learning, using a wide variety of methods including deep learning; (b) Logic- and knowledge-based approaches, including knowledge representation, inductive (logic) programming, knowledge bases, inference and deductive engines, (symbolic) reasoning and expert systems; (c) Statistical approaches, Bayesian estimation, search and optimization methods.
European Parliament. Directorate General for Parliamentary Research Services: Scientific Foresight Unit (STOA)	Artificial Intelligence in healthcare. Applications, risks, and ethical and societal impacts. (2022) [38]	Here we will first use the historical definition of AI, i.e. when a machine is able to mimic human intelligence or even surpass it to perform a given task such as prediction or reasoning [..] we will mostly focus on one subfield of AI that is dominant in the healthcare area, namely machine learning. ML is a subfield of AI and concerns the methods that learn to perform given tasks, such as prediction or classification, based on existing data.
Selected other international, European and national institutions		
International Standardization Organization / International Electrotechnical Commission (ISO/IEC) Joint Technical Committee 1/SC 42	Information technology – Vocabulary. (2015) ISO/IEC 2382:2015 [39] (revision under review)	Branch of computer science devoted to developing data processing systems that perform functions normally associated with human intelligence, such as reasoning, learning, and self-improvement.

(Continued)

Table 2. (Continued).

Organization/institution	Document details (title, year)	Verbatim extract from definition
ISO/IEC JTC 1 (on information technology)/Sub-committee 42 (on AI) [as above]	Information technology – Artificial intelligence – Artificial intelligence concepts and terminology. (2022) 2022–07 ISO/IEC 22989:2022 [40]	AI is a technical and scientific field devoted to the engineered system that generates outputs such as content, forecasts, recommendations or decisions for a given set of human-defined objectives.
IEEE Engineering in Medicine and Biology Society (EMBS) Artificial Intelligence Medical Devices Working Group [41] (EMB/Stds Com/AIMDWG)	IEEE Recommended practice for the quality management of datasets for medical artificial intelligence. (2022) IEEE 2801–2022 [42]	This identifies best practices for establishing a quality management system for datasets used for AI medical device, including data collection, transfer, utilization, storage, maintenance and update; and it lists critical factors that impact the quality of datasets.
Organisation for Economic Co-operation and Development OECD	OECD Science, Technology and Industry Scoreboard 2017: The Digital Transformation. [43]	AI is a term used to describe machines performing human-like cognitive functions (e.g. learning, understanding, reasoning or interacting).
OECD Council on Artificial Intelligence	OECD, Recommendation of the Council on Artificial Intelligence, OECD/LEGAL/0449. (2019) [44]	An AI system is a machine-based system that can, for a given set of human-defined objectives, make predictions, recommendations, or decisions influencing real or virtual environments. AI systems are designed to operate with varying levels of autonomy.
OECD Expert Group on Artificial Intelligence	Scoping the OECD AI principles: Deliberations of the Expert Group on Artificial Intelligence at the OECD (AIGO). (2019) OECD Digital Economy Papers No. 291. [45]	An AI system is a machine-based system that is capable of influencing the environment by producing an output (predictions, recommendations or decisions) for a given set of objectives. It uses machine and/or human-based data and inputs to (i) perceive real and/or virtual environments; (ii) abstract these perceptions into models through analysis in an automated manner (e.g. with machine learning), or manually; and (iii) use model inference to formulate options for outcomes.
OECD Committee on Digital Economy Policy	OECD Framework for the Classification of AI systems. (2022) OECD Digital Economy Papers, No. 323. [46]	AI models are actionable representations of all or part of the external context or environment of an AI system (encompassing, for example, processes, objects, ideas, people and/or interactions taking place in context). AI models use data and/or expert knowledge provided by humans and/or automated tools to represent, describe and interact with real or virtual environments.
World Health Organization	Ethics and governance of artificial intelligence for health. WHO guidance (2021) [47]	AI refers to the ability of algorithms encoded in technology to learn from data so that they can perform automated tasks without every step in the process having to be programmed explicitly by a human.
Food and Drug Administration, USA (FDA)	Proposed regulatory framework for modifications to artificial intelligence /machine learning (AI/ML)-based software as a medical device (SaMD). (2021) [48]	The IMDRF defines SaMD as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device. FDA [..] considers medical purpose as those purposes that are intended to treat, diagnose, cure, mitigate, or prevent disease or other conditions.

likely fall under Class IIa or higher. Application of the MDR will hopefully lead to an increase in clinical data supporting the safety and performance of these devices.

There is skepticism about some claims for medical applications of AI that are insufficiently supported by evidence, when systematic reviews have demonstrated that they can currently replicate the results of experts rather than exceed their performance. For example, external validation of diagnostic imaging tools resulted in a pooled sensitivity of 87%, compared with 92.5% for evaluation by experts [19]. In 2018 a Cochrane Collaboration review of 42 studies that used ML to diagnose skin cancer in adults found high sensitivity but low and variable specificity; the evidence base was considered too poor to understand any impact of the results on clinical decision-making, particularly in unselected subjects with a low prevalence of disease [20]. Applying AI clinical prediction models in 71 studies was equivalent to established statistical methods using logistic regression [21].

There are few prospective randomized trials of ML and the risk of bias is high [22–24]. Most reports do not include an analysis of performance errors [25]. A majority of studies have involved only a few centers, and when external validation has been undertaken it has shown a significant drop in the accuracy of the software [23,24]. To date, there is sparse evidence that the use of ML-based clinical decision support systems [26] is associated with improved clinician diagnostic performance [27]. The use of AI for predictive modeling is increasing but often insufficient details are published to support their external validation [28].

Similar questions could be raised about the reliability of clinical measurements and diagnoses made by humans. Their decisions may be based on incomplete, inaccurate or biased information [29], or taken when affected by fatigue or other human factors. For particular indications, AI medical devices may overcome some of these limitations and provide support for making diagnostic decisions. The critical question is whether the combination of human and machine (or more specifically, an AI algorithm) performs better and more efficiently than a human alone, for an intended clinical purpose.

There is widespread recognition that standards are needed to guide what evidence from clinical evaluation is needed for submissions for regulatory approval of AI applications in

healthcare. A proposal from the EU Horizon 2020 program that was published in 2019 stated that new medical technologies such as AI 'pose additional challenges and opportunities for developers to generate high-quality clinical evidence' [30]. It called for research to 'identify gaps to be filled' and to 'derive recommendations for the choice of clinical investigation methodology to obtain sufficient evidence' [30]. An overview of the concerted action now addressing that call has been published (CORE-MD, Coordinating Research and Evidence for Medical Devices) [31]. This review of regulatory initiatives has been conducted as part of the CORE-MD task on AI.

3. Definitions of artificial intelligence

In 2013 the IMDRF defined Software as a Medical Device (SaMD) in very general terms as any software designed for a medical purpose [32] (Table 2). Software utilizing AI is covered by the definition but only if it is not an essential component of a hardware device. In all its reports, the IMDRF Working Group on SaMD has stated that medical software does not meet its definition of SaMD if its intended medical purpose is to drive a hardware medical device – for software that is embedded in a medical device, other provisions apply. The IMDRF also does not mention the functions of prediction and prognosis in its definition of a medical device, although it states that SaMD may be an aid to prediction or prognosis (paragraph 5.2.3) [32].

Some regulatory agencies use the term SaMD which may be designated as 'stand-alone' although strictly speaking that is a misnomer since the software is always connected to or integrated within a digital device, computer or IT platform. Instead of SaMD, EU guidance uses the term MDSW [5] for software applications including those that incorporate AI or

ML algorithms. The FDA differentiates between SaMD and SiMD (Software in a Medical Device) [49] (Figure 1).

Early definitions of AI in Europe were developed for general rather than for healthcare applications. The European AI strategy refers to 'systems that display intelligent behaviour by analysing their environment and taking action – with some degree of autonomy – to achieve specific goals' [50]. Emphasis on autonomy is probably not relevant for most clinical AI applications since human agency and oversight are considered paramount [47] (although for some medical AI systems they may not be feasible or wanted).

For the objective of providing guidance to manufacturers and regulators on the clinical evaluation of AI in medical devices, we think that it is preferable not to restrict definitions according to the physical context in which particular software operates. In our opinion, it is more inclusive and useful for most purposes to refer to 'AI systems,' which is the term that was recommended by the EU High-Level Expert Group on AI (HLEG) in 2018 in its first report to the European Commission; an AI system was defined as any AI-based component, whether software and/or hardware, usually embedded as a component of a larger system [35].

In 2018 the European Commission established a knowledge service called AI Watch, managed by the EU Joint Research Centre from its site in Seville, which has responsibility for monitoring the development, uptake and impact of AI. One of its first reports referred to the absence of any standard definition, so AI Watch adopted the definition from HLEG (see Table 2) as the starting point for proposing a detailed taxonomy [6]. The document has been updated and now includes a comprehensive and highly informative summary of 69 definitions of AI that have been applied in various countries or proposed by academic authors [51].

Figure 1. Comparison of regulatory definitions of medical device software and their scope.

Sources: IMDRF: Software as a Medical Device, SaMD WG/N10, 2013 [32]. Also reviewed in [36]. EU: Medical Device Coordination Group. MDCG 2019–11: Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR [5]. FDA: Software as a Medical Device, and Software in a Medical Device: Content of Premarket Submissions for Device Software Functions – Draft Guidance for Industry and Food and Drug Administration Staff – 4 November 2021 (lines 180–7) [49].

The draft EU Regulation on Artificial Intelligence (AI Act) that was proposed in 2021 is now being reviewed by the European Parliament and Council [37]. The AI Act will apply across all sectors, but AI that qualifies as a medical device will also need to satisfy the requirements of the MDR. Neither the AI Act nor the MDR refers specifically to medical AI systems. The introduction to the AI Act states that uniformity and 'a single future-proof definition of AI' are needed. It is unclear to us if that will be achieved by this legislative definition since it specifies particular methodologies (in an annex) and those will evolve, but amendments have been proposed that if accepted would bring the EU AI Act definition in line with that proposed by OECD.

The most recent contribution to this debate within the EU has come from the scientific advisory service to the European Parliament (Science and Technical Options Assessment, STOA), which reverted to a historical definition [38] (see Table 2). On a wider stage, the Organisation for Economic Co-operation and Development (OECD) has an AI Policy Observatory that has published several reports, which give overlapping definitions. OECD is a voluntary collaboration of 38 member countries with no legal authority, yet its papers are influential [52] – the OECD definition has been cited by the World Health Organization (WHO) [47]. Note that the definition does not mention 'intelligence' (see Table 2: OECD Council on AI).

A consensus may develop but current definitions tend to be overelaborate and they have not yet converged into a version accepted by regulators worldwide. One of the most straightforward definitions, given by the AI pioneer Marvin Minsky in 1968 as 'the science of making machines do things that would require intelligence if done by men' [6], is appealing but begs the question of how to define intelligence. Features of human cognitive ability that are considered to correlate with intelligence include reasoning, memory, and processing speed [53,54]. Many recent advances in AI have been in the sub-discipline of ML, which involves building systems that can learn to solve problems without being explicitly programmed to do so. Another short and useful definition that would apply particularly to ML, was included in the executive summary of WHO guidance on the ethics and governance of AI: 'the ability of algorithms to learn from data so that they can perform automated tasks' (see Table 2 for the full quotation) [47].

3.1. Definitions of risks of AI medical devices

Suppose it is agreed that specifying each individual purpose of an AI system is much more important than having a unifying definition for AI MDSW. In that case, it is essential to establish criteria that should be used to identify which AI systems need more in-depth clinical investigation and most evidence of benefit before they are certified by a notified body and placed on the EU market. In 2014 the IMDRF guidance on SaMD identified two main dimensions of risk, which can be simplified as the function of the software and the severity of the disease [4]. SaMD should be designated in the highest-risk groups (called categories III and IV in that document) if it provides information used to diagnose or treat a disease, and if the healthcare situation is serious or critical [4]. The full list of factors identified in the IMDRF report as influencing risk, is given in Table 3. EU guidance from the MDCG gave illustrative examples for classification [5].

These documents have concerned MDSW in general, while recent guidance from the Chinese regulatory agency referred to AI-based MDSW specifically. It states that an AI system with 'low maturity in medical applications,' meaning that its safety and effectiveness have not been fully established, should be managed as a Class III medical device [defined as a high-risk medical device implanted into the human body, and used to support or sustain life] if it is going to be used 'to assist decision-making, such as providing lesion feature identification, lesion nature determination, medication guidance, and treatment plan formulation' [55]. If it is not used to aid decision-making, but rather for data processing or measurement that provides clinical reference information, then it will be managed as a Class II medical device. The UK regulatory agency envisages using a similar mechanism, called the 'airlock classification rule,' to assign class III to SaMD with a poorly understood risk profile [56]. The challenge for UK and Chinese policymakers is to translate 'sufficiently understood' or 'fully established safety' into a predictable and objective legal instrument. Equivalent clarity from all IMDRF regulators would be helpful.

Table 3. Factors influencing the risks of software as a medical device (SaMD).

Factors influencing the risks of software as a medical device (SaMD)
The type of disease or condition
Fragility of the patient with respect to the disease or condition
Progression of the disease or the stage of the disease/condition
Usability of the application
Designed towards a specific user type
Level of dependence or reliance by the user upon the output information
Ability of the user to detect an erroneous output information
Transparency of the inputs, outputs and methods to the user
Level of clinical evidence available and the confidence on the evidence
The type of output information and the level of influence on the clinical intervention
Complexity of the clinical model used to derive the output information
Known specificity of the output information
Maturity of clinical basis of the software and confidence in the output
Benefit of the output information vs. baseline
Technological characteristics of the platform the software are intended to operate on
Method of distribution of the software

From: IMDRF Software as a Medical Device (SaMD) Working Group. 'Software as a Medical Device': Possible Framework for Risk Categorization and Corresponding Considerations. IMDRF/SaMD WG/N12FINAL:2014 [4].

In the EU, Rule 11 in paragraph 6.3 of Annex VIII of the MDR, concerning classification, states that 'Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa, except if such decisions have an impact that may cause: death or an irreversible deterioration of a person's state of health, in which case it is in class III; or a serious deterioration of a person's state of health or a surgical intervention, in which case it is classified as class IIb. Software intended to monitor physiological processes is classified as class IIa, except if it is intended for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient, in which case it is classified as class IIb. All other software is classified as class I' [12].

4. Expert consensus recommendations

Ideally, regulatory and scientific requirements for evaluation should align. When appraising new technology, however, the focus of regulators and healthcare professionals is not always the same. Several academic initiatives have emerged to fill a perceived gap in guidance for evaluating AI robustly from a clinical perspective. They can be divided into three broad groups: methodological recommendations, tools to assess the risk of bias and/or quality, and reporting guidelines. The most authoritative guidelines so far were developed using Delphi processes and have focused on reporting, whereas methodological guidance has come from smaller expert groups or single research laboratories. Overall, the trend is toward a staged approach to evaluating AI through several preclinical and clinical assessment steps.

The first consensus statements on how to report AI studies came from the CONSORT-AI and SPIRIT-AI working groups in 2020. Their checklists focus respectively on randomized controlled trials and their protocol [57,58]. Then DECIDE-AI was published in May 2022, with an emphasis on the early-stage evaluation of AI decision-support systems when used in clinical settings where their recommendations have an impact on the patient's care [59]. These three checklists were developed by multi-stakeholder groups that included regulators in their feedback rounds and consensus meetings. They incorporate items that are needed for regulatory reviews, such as a clear

statement of the intended use, reporting of safety issues, and a description of the data-management process.

Two more cross-specialty AI reporting guidelines are being developed: TRIPOD-AI focusing on the development and validation of predictive models using AI [60], and STARD-AI concerning the diagnostic accuracy of AI-based diagnostic tools [61]. The TRIPOD-AI authors are also preparing the PROBAST-AI extension, which will be a 'risk of bias' assessment tool adapted specifically to AI studies [60].

Table 4 gives an overview of these current and forthcoming cross-specialty AI guidelines based on large consensus processes. Other initiatives based on systematic consensus methodology have published specialty-specific guidance [62–64] (Table 5). Reporting guidelines that are based on expert opinion, and additional recommendations for quality control of AI clinical tools, are also included in Table 5 [62–78], but the list is not exhaustive. For up-to-date information on existing and planned reporting guidelines, the EQUATOR network remains the source of choice [79].

Methodological development pathways have been proposed [63,65–70] but there is not yet a broad consensus on the most appropriate options. Overall, the suggested pathways often include an initial phase of *in silico* internal validation, followed by an external *in silico* validation, and then a phase of off-line or '*shadow mode*' fine-tuning to the context in which the AI system will be implemented. Thereafter, the performance of the AI should be assessed in the deployment settings without impacting patient care (i.e. in parallel but independently from standard clinical decision-making), before a phase of early *live* clinical evaluation (meaning in a situation where the recommendations of the AI systems have an actual impact on patient care). The recommended later stages would then be a large and possibly multicentric comparative evaluation, and finally, a phase of scaling up with adequate long-term monitoring, also coined by some as 'algorithmovigilance.' Table 6 summarizes the key components present in these consensus-based guidelines, which were also reviewed by Shelmerdine et al. [80].

Even if not aimed explicitly at medical AI, some other recommendations are worth noting. The framework from the Medical Research Council in the UK for developing and evaluating complex interventions [81], as well as the IDEAL framework for surgical innovation [82,83] and especially its

Table 4. Cross-specialty recommendations on medical AI, developed using a systematic expert consensus methodology.

ACRONYM	YEAR	PUBLICATION	TOPIC
Pre-clinical evaluation			
TRIPOD–AI	upcoming	BMJ Open (protocol) [60]	Reporting guideline for the development and validation of predictive models
PROBAST–AI	upcoming	BMJ Open (protocol) [60]	Risk of bias assessment tool for prediction models
STARD–AI	upcoming	BMJ Open (protocol) [61]	Reporting guideline for AI-centred diagnostic accuracy studies
Clinical evaluation			
DECIDE–AI	2022	● BMJ [59] [& joint publication in Nature Medicine]	Reporting guideline for the early stage, live clinical evaluation of decision support systems driven by artificial intelligence
SPIRIT–AI	2020	● BMJ [58] [& joint publication in Nature Medicine, and Lancet Digital Health]	Reporting guideline for clinical trial protocols of interventions involving artificial intelligence
CONSORT–AI	2020	● BMJ [57] [& joint publication in Nature Medicine, and Lancet Digital Health]	Reporting guidelines for clinical trial reports of interventions involving artificial intelligence

A repository of professional standards is available at: https://www.equator-network.org/

Table 5. Cross-specialty or specialty-specific recommendations on medical AI, published by medical associations or groups of investigators.

ACRONYM/FIRST AUTHOR	YEAR	PUBLICATION	SPECIALTY	TOPIC
Methodological guidelines				
Park	2020	JAMIA Open [65]	Cross-specialty	Recommendations for a phased approach to medical AI evaluation
Sendak	2020	EMJ Innovation [66] European Medical Journal	Cross-specialty	Recommendations for translation of ML products into healthcare delivery
McCradden	2020	Nature Medicine [67]	Cross-specialty	Recommendation for an ethical integration of healthcare AI
Higgins	2020	Advanced Intelligent Systems [68]	Cross-specialty	Framework for AI product development in healthcare
PRIME Sengupta	2020	JACC Cardiovascular Imaging [69]	Cardiology	Requirements for cardiovascular imaging-related ML evaluation §
Schwendicke*	2021	Journal of Dentistry [63]	Dentistry	Planning, conducting and reporting of AI studies in dental research §
FUTURE–AI Lekadir	2021	Arxiv (preprint) [70]	Radiology	Recommendations for trustworthy AI in medical imaging
Reporting guidelines				
MI-CLAIM Norgeot	2020	Nature Medicine [71]	Cross-specialty	Minimum information about clinical AI modeling
MINIMAR Hernandez-Boussard	2020	JAMIA [72]	Cross-specialty	MINimum Information for Medical AI Reporting
Sendak	2020	NPJ Digital Medicine [73]	Cross-specialty	ML model fact labels
CAIR Olczak	2021	Acta Orthopaedica [74]	Cross-specialty	Checklist for clinical AI research reporting
CLAIM Mongan	2020	Radiology: Artificial Intelligence [75]	Radiology	Artificial intelligence in medical imaging
Computer Vision in Surgery International Collaborative* Kitaguchi	N/A	Annals of Surgery [62]	Surgery	Proposal for assessment of surgical procedure and assistance using AI-based computer vision
Quality control				
Vollmer	2020	BMJ [76]	Cross-specialty	20 critical questions on transparency, replicability, ethics, and effectiveness
Scott	2020	BMJ Health and Care Informatics [77]	Cross-specialty	Checklist for suitability of machine learning applications in healthcare
OSCAR-AI Petzold	2021	Annals of Clinical and Translational Neurology [78]	Ophthalmology & neurology	Quality control criteria for AI-enhanced OCT applications
CLEAR Derm* Daneshjou	2021	JAMA Dermatology [64]	Dermatology	Checklist for evaluation of image-based AI algorithm reports in dermatology

§ a joint methodological and reporting guideline;
* developed through a systematic consensus methodology.

extension to medical devices [84], offer transferable guidance for the evaluation of clinical AI. A German medical device consultancy with expertise in medical software has developed guidance with colleagues from a German notified body; their detailed suggestions overlap with those of the professional consensus statements [85]. In the biological and life sciences, Heil et al. proposed reproducibility standards for ML [86] and Luo et al. published guidelines for developing and reporting ML predictive models [87]. A shared registry has been established, called AIMe, for investigators to provide transparent details of their AI biomedical applications [88].

A recent systematic review of 503 clinical diagnostic studies that had employed deep learning for medical imaging, found considerable heterogeneity between studies and extensive variation in methodology, terminology, and outcome measures [89]. The authors concluded that 'there is an immediate need for the development of AI-specific EQUATOR guidelines.' This need has now been answered, at least partially, since the professional recommendations listed in Tables 4 and 5 can be consulted and applied to inform best practice in clinical AI. Their shared features (see Table 6) could be considered by medical device regulators for incorporation into guidance or common specifications.

5. Guidance, standards, and common specifications for AI medical devices

Medical device legislation provides high-level requirements. The MDR contains 'General safety and performance requirements'

but it would be impractical to cover the wide variety of possible technologies and purposes individually. Instead, legislators expect that guidance, standards, or technical specifications will provide detailed advice for implementation.

For particular types of devices the EU relies on recommendations prepared by the global standards organizations – especially the ISO (International Organization for Standardization) and the IEC (International Electrotechnical Commission) – that were originally established to meet the needs of industry. Selected standards are harmonized by their equivalent European standards organizations CEN and CENELEC (Comité Européen de Normalization; and Comité Européen de Normalization Electrotechnique), which verify that they are concordant with any relevant EU laws. Their titles are then published in the Official Journal of the EU (OJEU); the first list of harmonized standards relating to the MDR appeared in July 2021 [90] and there have been two updates. So far, all the harmonized medical device standards are general; none relates specifically to AI.

Compliance with ISO standards and harmonized CEN and CENELEC standards is voluntary, although a legal case in 2016 established that harmonized standards that have been cited in the OJEU are a measure of EU law [91]. A manufacturer receives a 'presumption of conformity' with EU legal requirements for its device if it meets the specifications of the relevant harmonized standard. If international standards are not available, the European standards organizations may develop European-specific standards. In the absence of standards suitable for harmonization, the European Commission can issue common

Table 6. Key components of consensus-based guidelines.

Key AI components/criteria recommended for inclusion	TRIPOD-AI	PROBAST-AI	STARD-AI	DECIDE-AI [59]	SPIRIT-AI [58]	CONSORT-AI [57]	CLEAR Derm [64]	Schwendicke et al. [63]	Computer Vision in Surgery Int. Collab.
Intended use	Upcoming	Upcoming	Upcoming	X	X	X	X		Upcoming
Preexisting evidence				X	X				
Characteristics of training set, including sample size and class distribution				X			X	X	
Data acquisition process				X	X	X	X	X	
Missing or poor quality data				X	X	X		X	
Data preprocessing				X	X	X	X	X	
Computational resources and technical integration						X		X	
Model description, including versioning				X	X	X	X	X	
Training process, including dataset split				X			X	X	
Validation process				X			X	X	
Characteristics of study population and external dataset, including sample sizes and inclusion/exclusion criteria				X	X	X	X	X	
Characteristics of the user population				X					
Ground truth and labeling							X	X	
Characteristics of study settings				X	X	X	X		
Performance assessment				X	X	X	X	X	
Uncertainty				X				X	
Out-of-distribution results							X		
AI system output				X	X	X		X	
Explainability								X	
Benchmarking and comparison				X	X	X	X	X	
Clinical outcomes				X	X	X	X		
Integration in clinical pathway				X	X	X			
AI system iterative improvement				X					
Human factors evaluation				X	X	X			
Safety and errors				X	X	X			
Patient involvement				X					
Ethics and biases				X	X		X	X	
Data protection					X		X	X	
Code and data availability				X	X	X	X	X	
Funding				X	X	X		X	

specifications. For medical devices, this implies that the MDCG has the authority to write common specifications with input from expert panels and expert laboratories. The inter-relationships between standards organizations are illustrated in Figure 2, which also lists relevant initiatives engaged with the interoperability of information technology.

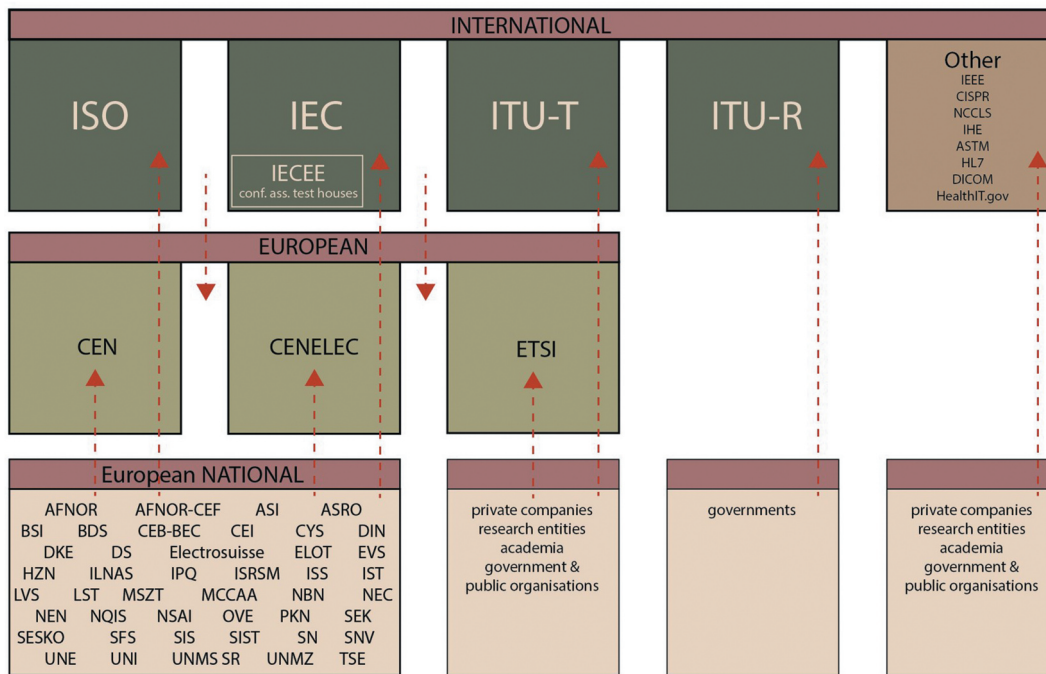## 5.1. International and European standardization bodies

The ISO and the IEC established a joint project on AI in 2018; formally, it is conducted by Sub-Committee 42 (on AI) of Joint Technical Committee 1 (on information technology), or ISO/IEC JTC 1/SC 42, with the secretariat being provided by the American National Standards Institute (ANSI). Working Groups (WG) of this committee have published 8 standards (Table 7), and at least 25 more are at different stages of preparation (Table 8). These foundational standards deal with general issues such as definitions (WG 1). None is focused on medical applications of AI but some may have relevance for medical devices, such as the first report from WG3 in 2020 on trustworthiness. In future, WG3 will work on methods for verifying the performance of neural networks [92].

For general guidance relating to medical devices, the EU regulatory system applies ISO 13485 about quality management systems [93], ISO standard 14,155 which describes the clinical investigation of medical devices [94] (or more correctly their equivalents EN ISO 13485:2016, and EN ISO 14155:2020, but note that only the first of these has been harmonized to the MDR), and ISO 14971 on risk management [95]. ISO 14155 recommends principles for clinical evaluation and mentions types of studies (in Annex I) but it does not prescribe particular methodologies or clinical trials whether for AI systems or any other type of medical device. A new and more specific ISO standard concerning clinical evaluation for medical devices has been proposed, to recommend methodologies for collecting and appraising clinical data across the full lifecycle of a device. If formally adopted, then responsibility for developing and producing the standard within 3 years will be passed to the same working group that prepared ISO 14155 (namely ISO/TC 194 WG4).

The European bodies CEN and CENELEC also have a joint technical committee on AI (Joint CEN-CENELEC Technical Committee 21 or CEN-CLC/JTC 21) that was created in 2021. A third EU standardization organization, called the European Telecommunications Standards Institute (ETSI), is the European equivalent of the Telecommunications sector of the International Technology Union (ITU-T). In addition to telecommunications and broadcasting, ETSI is concerned with standards for other electronic communication networks and services, and it has an Industry Specification Group on 'Securing Artificial Intelligence' and an Operational Coordination Group on AI. ETSI is recognized by the EU as the preferred partner for ICT standards supporting EU strategic objectives relating to health.

While the legislative process on the AI Act is continuing, the European Commission is seeking to speed up the development of harmonized standards and have them available by the time the regulation is applicable, which could be in late 2024 or early 2025.

Figure 2. A simplified landscape of the inter-relationships of European and global bodies engaged in the development of standards for AI medical devices.

Explanation of acronyms: ASTM International, American Society for Testing and Materials; CEN, Comité Européen de Normalization; CENELEC, Comité Européen de Normalization Electrotechnique; CISPR, Comité International Spécial des Perturbations Radioélectriques; DICOM, Digital Imaging and Communications in Medicine; ETSI, European Telecommunications Standards Institute; HealthIT.gov, website of the Office of the National Coordinator for Health Information Technology (ONC), U.S. Department of Health and Human Services; HL7, Health Level Seven International; IEC, International Electrotechnical Commission; IECEE, IEC System of Conformity Assessment Schemes for Electrotechnical Equipment and Components; IHE International, Integrating the Healthcare Enterprise; ISO, International Standardization Organization; ITU-R, ITU Radiocommunication Sector; IEEE, Institute of Electrical and Electronics Engineers; ITU-T, International Telecommunication UnionTelecommunication Standardization Sector; NCCLS, National Committee for Clinical Laboratory Standards (now known as Clinical and Laboratory Standards Institute (CLSI); Details of the European National Standardization Bodies listed in the bottom left box are given at the website of CEN/CENELEC: https://standards.cencenelec.eu/dyn/www/f?p=CEN:5

Table 7. Information technology standards relating to general aspects of AI, that have already been published.

Publication Date	Reference	Title
2022–07	ISO/IEC 22989:2022	Information technology – Artificial intelligence – Artificial intelligence concepts and terminology
2022–06	ISO/IEC 23053:2022	Framework for Artificial Intelligence (AI) Systems Using Machine Learning (ML)
2022–05	IEEE 2801–2022	IEEE Recommended Practice for the Quality Management of Datasets for Medical Artificial Intelligence
2021–12	ISO/IEC TR 24372:2021	Information technology – Artificial intelligence (AI) – Overview of computational approaches for AI systems
2021–11	ISO/IEC TR 24027:2021	Information technology – Artificial intelligence (AI) – Bias in AI systems and AI aided decision making
2021–05	ISO/IEC TR 24030:2021	Information technology – Artificial intelligence (AI) – Use cases
2021–03	ISO/IEC TR 24029–1:2021	Artificial Intelligence (AI) – Assessment of the robustness of neural networks – Part 1: Overview
2020–05	ISO/IEC TR 24028:2020	Information technology – Artificial intelligence – Overview of trustworthiness in artificial intelligence

Details obtained from https://www.iso.org/ics/35.020/x/
(accessed week of 18 July 2022)

To this aim, on 20 May 2022 the Commission issued a draft standardization request to CEN, CENELEC, and ETSI in support of safe and trustworthy AI [96]. CEN and CENELEC have responded by setting up a Standardization Request Ad Hoc Group (SRAHG) on AI.

A comprehensive overview and comparison of the contents and recommendations of international standards relevant to AI was prepared for AI Watch in the EU [97].

5.2. The Institute of Electrical and Electronics Engineers (IEEE)

The division of IEEE that is most relevant for medicine is the IEEE Engineering in Medicine and Biology Society (EMB). It has a Standards Committee (EMB-SC) which recommends engineering practices to be followed by electrical and electronic manufacturers and health care providers. IEEE prefers

to use the term autonomous and intelligent systems (A/IS), rather than AI which it considers too vague [10]. There is a standard that specifies taxonomy and definitions for human augmentation, which refers to technologies including many implants and wearables that enhance human capability. IEEE also has a global initiative on the ethics of A/IS, whether they are physical robots or software such as medical diagnostic systems [10]. Table 9 lists some IEEE projects that are developing guidance on medical AI.

6. Initiatives of medical device regulators and intergovernmental organizations

The promotion of AI has become a political priority, with countries competing to become global leaders [98,99]. The trend has been accompanied by a growing recognition that AI needs

Table 8. General standards under joint development by the International Standardization Organization (ISO) and the International Electrotechnical Commission (IEC), related to artificial intelligence.

Reference	Title
ISO/IEC PRF TS 4213	Information technology – Artificial Intelligence – Assessment of machine learning classification performance
ISO/IEC AWI 5259–1	Artificial intelligence – Data quality for analytics and machine learning (ML) – Part 1: Overview, terminology, and examples
ISO/IEC AWI 5259–2	Artificial intelligence – Data quality for analytics and machine learning (ML) – Part 2: Data quality measures
ISO/IEC AWI 5259–3	Artificial intelligence – Data quality for analytics and machine learning (ML) – Part 3: Data quality management requirements and guidelines
ISO/IEC AWI 5259–4	Artificial intelligence – Data quality for analytics and machine learning (ML) – Part 4: Data quality process framework
ISO/IEC AWI 5259–5	Artificial intelligence – Data quality for analytics and machine learning (ML) – Part 5: Data quality governance
ISO/IEC CD 5338	Information technology – Artificial intelligence – AI system life cycle processes
ISO/IEC CD 5339	Information Technology – Artificial Intelligence – Guidelines for AI applications
ISO/IEC CD 5392	Information technology – Artificial intelligence – Reference architecture of knowledge engineering
ISO/IEC DTR 5469	Artificial intelligence – Functional safety and AI systems
ISO/IEC AWI TS 5471	Artificial intelligence – Quality evaluation guidelines for AI systems
ISO/IEC DIS 8183	Information technology – Artificial intelligence – Data life cycle framework
ISO/IEC AWI TS 8200	Information technology – Artificial intelligence – Controllability of automated artificial intelligence systems
ISO/IEC AWI TS 6254	Information technology – Artificial intelligence – Objectives and approaches for explainability of ML models and AI systems
ISO/IEC AWI TS 12791	Information technology – Artificial intelligence – Treatment of unwanted bias in classification and regression machine learning tasks
ISO/IEC AWI 12792	Information technology – Artificial intelligence – Transparency taxonomy of AI systems
ISO/IEC AWI TR 17903	Information technology – Artificial intelligence – Overview of machine learning computing devices
ISO/IEC DIS 23894	Information technology – Artificial intelligence – Guidance on risk management
ISO/IEC DIS 24029–2	Artificial intelligence (AI) – Assessment of the robustness of neural networks – Part 2: Methodology for the use of formal methods
ISO/IEC AWI TR 24030	Information technology – Artificial intelligence (AI) – Use cases
ISO/IEC TR 24368	Information technology – Artificial intelligence – Overview of ethical and societal concerns
ISO/IEC FDIS 24668	Information technology – Artificial intelligence – Process management framework for big data analytics
ISO/IEC DIS 25059	Software engineering – Systems and software Quality Requirements and Evaluation (SQuaRE) – Quality model for AI systems
ISO/IEC AWI TS 29119–11	Information technology – Artificial intelligence – Testing for AI systems – Part 11:
ISO/IEC CD 42001.2	Information Technology – Artificial intelligence – Management system
And in development by other TCs:	
ISO/IEC CD TR 27563	Security and privacy in artificial intelligence use cases

Details obtained from https://www.iso.org/committee/6794475/x/catalogue/p/0/u/1/w/0/d/0
(accessed week of 18 July 2022)

regulation, so now international and national regulatory bodies, academic institutions, and other organizations are developing standards and guidance. A voluntary registry maintained by IEEE, called OCEANIS (Open Community for Ethics in Autonomous and Intelligent Systems) currently lists 77 documents [100]. Many initiatives are not explicitly related to medical devices and those that mainly provide general recommendations overlap significantly. We understand that practical elements to guide the manufacturer, procurer, and user of medical AI systems are most clear in IMDRF, FDA, and NMPA (National Medical Products Administration of China) documents.

The following paragraphs and Table 9 provide an overview of some current initiatives, with a focus on global projects and those of particular relevance to the European Union.

6.1. International Medical Device Regulators Forum

The IMDRF Working Group on SaMD published its first report in 2013, on definitions, and then a framework for regulatory evaluation, in 2014 [4]. It states that the transparency of inputs used and the technological characteristics 'do not influence the determination of the category of SaMD' [4]. Its recommendation that regulators should consider SaMD according to the context in which it is used and the risks of its use has become widely accepted. The two criteria that should be applied were summarized in their 2017 recommendations on clinical evaluation, as the 'intended medical purpose' (whether to treat or diagnose/drive clinical management/or inform clinical management) and the 'targeted healthcare situation' (whether critical/serious/or non-serious) [33]. For the verification of product performance,

the IMDRF specifies under analytical and technical validation 'accuracy, reliability, (and) precision'; and for clinical validation, it refers to 'sensitivity, specificity, (and) odds ratio.'

The SaMD Working Group completed its tasks but has been reinstated so that it can revise the IMDRF guidance. Another IMDRF working group, on Artificial Intelligence-based Medical Devices, has considered key terms and definitions for ML-enabled medical devices. The EU participates through delegates from the Danish, German, French and Portuguese national regulatory agencies, with a policy officer from the European Commission.

6.2. World Health Organization

The WHO secretariat and members have agreed on six principles that should be followed to ensure that AI works for the public interest in all countries, limiting risks and maximizing the opportunities intrinsic to its use for health. For AI regulation and governance, these include protecting human autonomy and ensuring transparency, explainability and intelligibility [47].

There is a joint initiative between WHO and ITU, called the ITU-WHO Focus Group on Artificial Intelligence for Health (FG-AI4H). The topics on its agenda include regulatory best practices and specification of requirements. The group 'has tasked itself' to work toward creating evaluation standards [123,124].

6.3. European Union

The Directorate-General for Health and Food Safety of the European Commission (DG SANTE) coordinates the

Table 9. Selected regulatory initiatives and proposals under development.

Organization/committee	Task/project	Details/objectives
International Medical Device Regulators Forum (IMDRF)		
IMDRF SaMD Working Group	"Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations. (2014) [4]	Two major factors together provide a description of the intended use of SaMD, and can categorize it: "A. Significance of the information provided by the SaMD to the healthcare decision, and B. State of the healthcare situation or condition."
IMDRF SaMD Working Group	Software as a medical device: clinical evaluation. (2017) [33]	Pre-market: the manufacturer generates evidence of the product's accuracy, specificity, sensitivity, reliability, limitations, and scope.
IMDRF AI Working Group	IMDRF/AIMD WG (PD1)/N67:2021. Machine Learning-enabled Medical Devices – A subset of Artificial Intelligence-enabled Medical Devices: Key Terms and Definitions. (2021) [34]	Proposed definitions to complement earlier IMDRF documents on SaMD. A Machine Learning-enabled Medical Device (MLMD) is "a medical device that uses machine learning, in part or in whole, to achieve its intended medical purpose."
European Union		
European Commission, Medical Device Coordination Group	MDCG 2019–11. Guidance on qualification and classification of software in Regulation (EU) 2017/745 MDR & Regulation (EU) 2017/746 IVDR.	Rule 11 MDR describes the classification of medical device software. The details are quoted in the text of this paper, section 3.1 (see [5]).
AI Watch [101] Joint Research Centre, European Commission, Seville	60 papers published as of September 2022.	Review of initiatives for standardization of AI in the EU. (Nativi S et al. 2021 [97]; updated in 2022)
European Medicines Agency (EMA)	Regulatory Science, Research Needs (2021) [102]	Objective H2.7.7 = Identify and define regulatory requirements to validate AI algorithms used in the context of regulated medicines.
EMA with HMA (Heads of Medicines Agencies)	Accelerating Clinical Trials in the EU (ACT EU) (2022) [103]	Priority action 8 = Develop and publish key methodologies guidance e.g. on AI/ML impacted clinical trials
European Parliament. Directorate General for Parliamentary Research Services. Scientific Foresight Unit (STOA)	A governance framework for algorithmic accountability and transparency. (2019) [104]	Policy options for regulatory oversight, legal liability, and global coordination. For transparency, understanding how a system behaves is more important than knowing how it works.
European Parliament. Directorate General for Parliamentary Research Services: Scientific Foresight Unit (STOA)	Artificial Intelligence in healthcare. Applications, risks, and ethical and societal impacts. (2022) [38]	Identifies 7 main risks of AI in healthcare including bias and error. Recommends extended regulatory frameworks and codes of practice for medical AI, to assess algorithmic fairness, clinical safety, clinical acceptance, transparency and traceability.
Other European organizations		
OECD. AI Policy Observatory [105]	The OECD AI principles were adopted in 2019.	The Observatory provides a center for collecting and sharing evidence on AI.
Council of Europe Ad Hoc Committee on AI (CAHAI) [106]	Succeeded in 2022 by the Committee on Artificial Intelligence (CAI) [107]. Terms of reference not public.	The agenda of CAI includes consideration of legal instruments for risk and impact assessment.
Council of Europe [108] Steering Committee for Human Rights in the fields of Biomedicine and Health (CDBIO)	The impact of artificial intelligence on the doctor-patient relationship. Report prepared by Brent Mittelstadt, Anonymized. (2021) [109] CDBIO now has a drafting group on AI in healthcare.	The potential human rights impact of AI on the doctor-patient relationship can be categorized according to six themes: • Inequality in access to high quality healthcare • Transparency to health professionals and patients • Risk of social bias in AI systems • Dilution of the patient's account of well-being • Risk of automation bias, de-skilling, and displaced liability • Impact on the right to privacy
CEN-CENELEC Joint Technical Committee 21 'Artificial Intelligence' [110] (Secretariat held by DS, the Danish Standardization Body)	CEN-CENELEC Work Programme 2022 (page 30) [111]	JTC 21 will produce standardization deliverables to address European market and societal needs and to underpin legislation and policies based on the EU's principles and values: the objective is to contribute to the development of an ethical, human-centered and trustworthy AI from which all EU citizens can benefit.
Global organizations		
World Health Organization	Ethics and governance of artificial intelligence for health (2021) [47]	6 principles for the use of AI for health: • Protecting human autonomy. • Promoting human well-being and safety and the public interest. • Ensuring transparency, explainability and intelligibility. • Fostering responsibility and accountability. • Ensuring inclusiveness and equity. • Promoting AI that is responsive and sustainable
WHO/ITU-T Focus Group on Artificial Intelligence for Health (FG-AI4H)	Established in 2018. Goals include facilitating global dialogue for AI for health, and developing national guidance documents to ensure the safe and appropriate use of AI in health [112].	Working Groups include Regulatory considerations on AI for health, and Clinical evaluation of AI for health', to establish a standardized assessment framework for the evaluation of AI-based methods for health, diagnosis, triage or treatment decisions [113].

(Continued)

Table 9. (Continued).

Organization/committee	Task/project	Details/objectives
International Standardization Organization ISO ISO/IEC JTC 1/SC 42 Artificial Intelligence [114]	ISO created a standardization project on AI in 2017, that has been operational since 2018.	See Zielke et al for description of project [92]. 25 standards listed in development.
International Electrotechnical Commission (IEC)	62/411/NP: Testing of Artificial Intelligence/Machine Learning-enabled Medical Devices [115]	IEC 63450 in development, publication foreseen in 2024.
IEC	PWI 62–3 ED1: Publication due in 2022.	Artificial Intelligence/Machine Learning-enabled Medical Device – Performance Evaluation Process [116]
IEEE Engineering in Medicine and Biology Society (EMBS)		
IEEE P2673 Intelligence Augmentation for Medical Imaging Working Group [117]	Standard for patient digital biomedical data files with 3D topological mapping of macroanatomy and microanatomy for use in big data and augmented intelligence systems (in development)	Framework for organization and use of new patient biomedical files containing medical imaging and imaging biomarker information for use in big data cloud-based augmented intelligence systems.
EMBS Artificial Intelligence Medical Devices Working Group [118] (EMB/Stds Com/AIMDWG)	IEEE 2801–2022 [119,120]. Recommended practice for the quality management of datasets for medical artificial intelligence. (2022)	Best practices for establishing quality management system for datasets used for AI medical devices, and critical factors that impact the quality of datasets.
Artificial Intelligence Medical Devices Working Group	Standard for the performance and safety evaluation of artificial intelligence based medical device: Terminology. New IEEE standard (IEEE P2802) [121,122].	Definitions of fundamental concepts and methodology that describe the safety, effectiveness, risks and quality management of AI medical devices. It also establishes a vocabulary for the development of future standards for AI medical devices.

implementation of the MDR. Unit D3 (Medical Devices) collaborates with national regulators through the MDCG, which has a working group on New Technologies that is composed of competent authorities (regulatory agencies) from the Member States, and which is attended by delegates from stakeholder organizations including some European medical professional associations. Its terms of reference include responsibility for advising on the regulation of MDSW [125] and its work programme includes exploration of the need for guidance on MDSW that is intended to treat, and on requirements for AI devices.

The European Medicines Agency (EMA) has similar responsibilities relating to pharmaceutical products. The exploitation of AI in decision-making is one of its strategic goals, and the development of methodological guidance for AI in clinical trials is one of its priority actions (see Table 9) [126,127]. EMA is a member of the International Coalition of Medicines Regulatory Authorities (ICMRA) which recommended in a report on AI in 2021 that 'Regulatory guidelines for AI development, validation and use with medicinal products should be developed in areas such as data provenance, reliability, transparency and understandability, pharmacovigilance, and real-world monitoring of patient functioning' [128]. That agenda is remarkably similar to the tasks being set by medical device regulators. The ICMRA report even used as its example an app (rather than a drug), and it cited IMDRF documents and identified 'a need to establish clear mechanisms for regulatory cooperation between medicines and medical device competent authorities and notified bodies to facilitate the oversight of AI-based software intended for use in conjunction with medicinal products' [128].

The role of the Scientific Foresight Unit of the European Parliament is to provide expert scientific advice to members of the European Parliament (MEPs), through their Panel for the Future of Science and Technology (STOA). At a meeting in January 2020, STOA launched its Centre for AI (C4AI) with a mandate to provide strategic advice to MEPs until the end of the current European parliamentary term in 2024 [129]. Already in April 2019, STOA had proposed a governance framework for algorithmic accountability and transparency [104], and during 2022 it has prepared policy options for data governance [130] and a report on the applications, risks, and ethical and societal impacts of AI in healthcare [38]. The C4AI publishes briefing documents, and has launched a 'Partnership on AI' with the OECD Global Parliamentary Network.

The EU AI Watch has been productive. Its publications include an overview of the landscape of standardization for AI in Europe [97] and reports on AI applications in medicine and healthcare [131] and their uptake [132]. AI Watch has identified nine international standards that can support the proposed AI Act [97].

The European Commission appointed 52 experts to form the High-Level Expert Group on Artificial Intelligence (HLEG). Its report on ethics made general recommendations and referred to autonomous AI for 'deciding the best action(s)' [11]. It referred to the potential of AI to improve health and well-being, with examples (in footnotes) based on assumptions that earlier or more precise diagnosis would translate into better outcomes or more targeted treatments or more lives saved. The horizontal approach taken by the HLEG needs to be supplemented by recommendations for clinical AI tools, that should be prepared with the active involvement of medical experts and propose standards against which such assumptions could be tested. The HLEG also prepared a tool for assessing AI, with more than 100 questions on human agency and oversight, technical robustness and safety, privacy and data governance, transparency, diversity, nondiscrimination and fairness, societal and environmental well-being, and accountability [133].

6.4. Organisation for Economic Co-operation and Development

The OECD AI Policy Observatory report in 2019, known as the OECD AI Principles [45], was the first intergovernmental standard on AI and it provided the basis for the 2019 G20 AI Principles. They are relatively nonspecific but include

transparency, explainability, and accountability. Their implementation was recently reviewed by an OECD working group on national AI policies [134].

A Working Party on Artificial Intelligence Governance (WP AIGO) was created by OECD in March 2022, with members including a Legal and Policy Officer from the European Commission (Directorate-General for Communications Networks, Content and Technology, DG CNECT). The AIGO mandate until the end of 2023 includes supporting the implementation of OECD standards relating to AI, and developing tools, methods and guidance to advance the responsible stewardship of trustworthy AI [135]. The tasks are not focussed on clinical applications of AI, and the working party will report to the OECD Committee on Digital Economy Policy. It will cooperate with other international organizations and initiatives with complementary activities on AI, including the Global Partnership on AI (GPAI), the Council of Europe, and the United Nations Educational, Scientific and Cultural Organization (UNESCO).

6.5. The Council of Europe

The Council of Europe is an international organization that was founded in 1949 in the wake of the second world war to uphold human rights, democracy and the rule of law. It has a broader reach than the EU and now includes 46 member states. It has a committee (Council of Ministers) that needs to be distinguished from the European Council (of ministers) of the EU.

In September 2019, the Council of Europe set up an Ad Hoc Committee on Artificial Intelligence (CAHAI), which has now been succeeded by a permanent Committee on Artificial Intelligence (CAI). In a recent commentary, one of their directors stated that 'we clearly need regulation to leave essential decision-making to humans and not to mathematical models, whose adequacy and biases are not controlled' [136]. The strategic agenda of the Council of Europe will therefore include, by 2028, the issue of AI regulation 'in order to find a fair balance between the benefits of technological progress and the protection of our fundamental values' [136].

Among other reports, CAHAI proposed elements for a legal framework on AI such as the right to be informed about the application of an AI system in the decision-making process; and the right to choose interaction with a human in addition to or instead of an AI system [137] (see Table 9). In 2020 the Council of Ministers of the Council of Europe adopted a recommendation that each country should develop appropriate legislative, regulatory and supervisory frameworks, and it called for effective cooperation with the academic community [138]. In 2022 the Steering Committee for Human Rights in the fields of Biomedicine and Health (CDBIO) of the Council of Europe commissioned a technical report and set up a drafting group to consider AI in healthcare and in particular its impact on the doctor-patient relationship [109].

6.6. National regulatory agencies

Initiatives by national regulatory agencies related to the general governance of AI systems are too numerous to mention here. They have been summarized, for example in 2018 by Access Now, which is a global nonprofit organization [139], in 2019 by the OECD AI Policy Observatory which prepared 'country dashboards' [140], and in 2022 by AI Watch which reported that 24 EU countries already have their own national policies on standards, with health a high priority [141].

As an example of national approaches to AI in healthcare, UK standards for digital health technologies from the National Institute for Health and Care Excellence (NICE) have been updated [142]. They are relevant for SaMD applications including AI but not for software incorporated in medical devices. The British Standards Institution (BSI) will publish guidance that it has prepared together with the Association for the Advancement of Medical Instrumentation (AAMI) in the USA, on the application of ISO standard 14,971 (risk management) to AI [143]. The Medicines and Healthcare products Regulatory Agency (MHRA) with the FDA and Health Canada recently identified guiding principles for Good Machine Learning Practice for Medical Device Development [144].

In the USA, the FDA has proposed a total product lifecycle (TPLC) regulatory approach to AI – and ML–based SaMD. Its principles include initial premarket assurance of safety and effectiveness, SaMD prespecifications (SPS), an algorithm change protocol (ACP), transparency, and monitoring of real-world performance (RWP). The paper in April 2019 on a 'Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning-Based Software as a Medical Device' [48] has been influential. After public consultation, the FDA published its response in 2021 with an action plan that includes a tailored regulatory framework for AI–ML–based SaMD and the design of regulatory science methods 'to eliminate algorithm bias and increase robustness' [145]. A detailed review of US legislation relevant to AI medical devices was published by the National Academy of Medicine [146].

The Therapeutic Goods Administration (TGA) in Australia revised its approach, in 2021. The new guidance does not specify applications using AI or ML separately from other software as a medical device [147]. It reinforced essential principles for the clinical evaluation of high-risk devices and added special criteria such as transparency and version tracking. Any SaMD applications that are autonomous or which do not allow interpretation or oversight by a clinician of diagnoses or therapeutic recommendations are designated as high-risk [148].

The Chinese government recognizes the development of AI as an essential component of its national strategy [149] and it is developing a national AI standardization subcommittee (SAC/TC28/SC42) led by the China Electronic Standardization Institute (CESI) under the Ministry of Industry and Information Technology (MIIT). This subcommittee participates in ISO/IEC JTC1 SC42 activities on behalf of China [150]. There are three approaches to the general governance of AI: the Cyberspace Administration of China is responsible for rules for online algorithms, the China Academy of Information and Communications Technology for tools for testing and certification of 'trustworthy AI' systems, and the Ministry of Science and Technology for establishing AI ethics principles and review boards. Regulatory documents and standards have been published for AI medical devices by the NMPA, but they are not provided in English translations. The implementation of software risk management activities shall be based on

the intended use of software (target disease, clinical use, degree of importance, and degree of urgency), usage scenarios (target population, target users, place of use, clinical procedures), and core functions (objects of processing, data compatibility, type of function) and shall be performed throughout the life cycle of the software.

7. European laws with relevance to AI medical devices

Several EU laws may impact how medical AI systems can be used or how much information can or must be disclosed. Their provisions may have to be considered when developing EU guidance on reporting clinical evidence for AI as a medical device.

7.1. Freedom of access to information

The principle that information about clinical evidence for medical devices must be publicly accessible [151] was mentioned as a key element of the reform of the EU regulations. Recital 43 of the MDR states that 'transparency and adequate access to information [...] are essential in the public interest, to protect public health, to empower patients and healthcare professionals and to enable them to make informed decisions' [12]. Since EU notified bodies are independent companies, however, they are excluded from the provisions of the EU legislation on freedom of access to documents [152].

The opinions of the Expert Panels which provide independent scientific review of the Clinical Evaluation Assessment Reports prepared by notified bodies, are now being published by the European Commission with the name of the individual medical device and parts of the content redacted – despite the fact that the EMA, which is managing the panels, is an agency of the European Commission and therefore subject to the law on freedom of access. The specific name of a device is published later, but only if it has been granted a certificate of conformity. Further legal opinion and clarification of the law may be needed, or this interpretation may need to be contested.

7.2. The AI act proposal

The EU AI Act proposes to regulate high-risk AI systems that could have an adverse impact on the safety or fundamental rights of people [153]. Unless its text is amended, providers of high-risk AI systems (most likely manufacturers of AI medical devices [154]) will have to register them in the EU database before placing them on the market. As part of their conformity assessment for the MDR, AI medical devices will have to comply with requirements dealing with risk management and quality criteria concerning the training, validation, and testing of data sets. Manufacturers will have to provide technical documents describing compliance with applicable rules and keep records that ensure an appropriate level of traceability of the system's functioning including accuracy, robustness, and cybersecurity throughout its lifecycle. This is intended to enable users to interpret the output and have human oversight of an AI system. An AI medical device will fall within the Act's scope if a notified body is involved in its conformity assessment under sectorial legislation.

7.3. Data laws

The EU General Data Protection Regulation (GDPR) [155] sets horizontal rules, which apply to medical devices that process personal data. Guidance from the EU Data Protection Board has clarified how the GDPR relates to the analysis of clinical data for research [156]. The rules of the GDPR that are most relevant to the processing of personal data by AI systems in healthcare include Article 9 concerning the processing of special categories of personal data (which include health data and data concerning health) and Articles 13–15 which establish rights to 'meaningful information about the logic involved' in automated decisions made by AI.

The European Commission has recently initiated reforms concerning the regulation of data, including the Data Governance Act (DGA) [157] and proposals for a European Health Data Space (EHDS) [158] and a Data Act [159]. The DGA was approved in 2022 and will become applicable from September 2023; its objective is to foster the availability of data for use in the economy and society, including in healthcare settings. The EHDS proposal was published in May 2022; its objectives include regulating the sharing of electronic health data. It sets additional personal rights and mechanisms designed to complement those already provided under the GDPR for electronic health data. The Data Act proposal is aimed to apply horizontally also to medical and health devices (Recital 14) [160]; the proposal includes harmonized rules on fair access to and use of (health) data for the so-called relationships of 'business to consumer,' 'business to business,' and 'business to government.' Transposed to the medical device environment, it implies that new rules could govern access to data and its sharing between medical device manufacturers and hospitals or patients, among manufacturers themselves, or from manufacturers to public health bodies.

7.4. Intellectual property rights

There is a European Parliament resolution of 20 October 2020 on intellectual property rights for AI technologies [161]. The European Patent Organization (EPO) manages a long- and well-established system in Europe that has a category known as computer-implemented inventions (CII). Mathematical models and algorithms are not patentable under the European Patent Convention, but technical aspects of AI inventions are generally patentable as a subgroup of CII [162]. Source code could be copyrighted. Trade secrets may provide the broadest scope of IP protection. There may be tensions between some of these legal provisions and the need for transparency about the function and outcomes of AI applications used in clinical practice.

7.5. Liability laws

Liability laws protect individuals from defects in manufactured products. In the EU, this has been regulated since 1985 through Directive 85/374/EEC on liability for defective products [163]. EU Directives as legal instruments require implementation by the Member States, so liability schemes usually depend on national laws and their doctrinal and judicial

orientations. The Directive sets general rules of strict liability that are relevant to medical devices, and it has served as an interpretative basis for claims by patients [164,165]. It is under review after the European Commission set up an expert group to advise on liability law and challenges relating to the complexity, openness, autonomy, predictability, data-drivenness or vulnerability of new technologies [166].

With regard to the risks created by emerging digital technologies, the EU Expert Group noted in its 2019 report that the existing rules on liability offer solutions which do 'not always seem appropriate' [167]. Later, the European Commission issued a 'Report on the safety and liability implications of artificial intelligence, the internet of things and robotics' which highlighted legal fragmentation across Europe concerning liability paradigms as applied to AI, the complexity of digital ecosystems, and the plurality of actors involved [168]. It stated that this situation 'could make it difficult to assess where a potential damage originates and which person is liable for it' [168]. Further studies have commented on possible shortcomings of AI liability and on the European Commission's reports and initiatives [166,169]. Following a public consultation, the Commission has proposed a new AI Liability Directive to harmonize national liability rules [170].

7.6. Cybersecurity of AI medical devices

Ensuring the cybersecurity of AI medical devices and the healthcare systems of which they are a part is crucial to maintaining patients' health and safety [171]. In 2019 the MDCG issued the first EU guidance on medical device cybersecurity [172], but the first EU-wide general cybersecurity legislation was the Network and Information Security Directive (NIS Directive) of 2016 [173]. Its aim is to enhance the security of entities providing digital or essential services, which includes healthcare service providers that Member States have recognized as Operators of Essential Services (OES). The EU has proposed to recast the NIS Directive to expand the scope of its application to include medical devices, in which case security measures and risk management obligations would apply to medical device manufacturers. In addition, in 2019 the Cybersecurity Act (CSA) strengthened the role and tasks of the EU Agency for Cybersecurity (known as ENISA) and established a new cybersecurity certification framework for products and services [174]. The Radio Equipment Directive also applies in certain circumstances to medical devices [171,175] and Article 32 of the GDPR is relevant to the security of data processing [171].

8. Transparency and interpretability of AI medical device software

The transparency and interpretability of AI systems are key determinants of risk that should be factored into regulatory processes and decisions, but neither has a universally accepted definition, and the terms are often used interchangeably in the literature. Transparency was one of the seven key requirements for trustworthy AI identified by the EU HLEG [11].

8.1. Transparency

Transparency may be defined as the availability of information about each component of an AI system, namely the training data, the model structure, the algorithms used for training, deployment, pre- and post-processing of data, and the objective function of the AI system. Transparency has been proposed as a fundamental principle for the ethical use of AI [176] since it allows the performance of an AI system to be characterized across a range of conditions and it enables both regulatory audits and the identification of vulnerabilities and biases [104].

A system might be made fully transparent by openly publishing all relevant details including the data and programme code, but sometimes that may be unnecessary and/or unfeasible. The privacy of patients' clinical data must be protected, for example by ensuring secure encryption before data are transmitted or by using a distributed or federated analysis when data are combined for reporting the performance of an AI device. A compromise may need to be struck for commercial applications to protect intellectual property. Transparency is important and can be necessary for patients, so it would be useful to have consensus on when they should be informed that AI is being used [177].

Regulators who assess the clinical evidence presented for an AI system should focus firstly on the transparency of the data and methods, which is vital for determining the strength of the research methodology and the results presented, and secondly on how thoroughly it has been evaluated. It may not be essential to understand every aspect of the detailed methods for specific measurement tasks, as long as the training data are characterized for example with details of inclusion and exclusion criteria, demographic and relevant physiological characteristics, and as long as the model's performance is fully reported. A review of open-access datasets used to develop AI tools for diagnosing eye diseases showed poor availability of sufficient metadata [178].

8.2. Interpretability

Full transparency of methods is a precondition for interpretability [179]. We consider an interpretable system to be one that a human with relevant knowledge and experience can understand. The degree of interpretability ranges from a global understanding of the inner workings of a system, to the ability to understand each individual prediction made by the AI system. A more interpretable model poses less risk as it could allow human oversight and easier identification of errors. Consider, for example, an AI system for measuring the volume of tumors on a computed tomography (CT) scan. An end-to-end solution that presents only a numeric value lacks interpretability, but if intermediate results are presented such as an illustration of the AI delineation (segmentation) of the tumor, then it is more easily interpretable by a clinician. This approach also allows the assignment of accountability to the interpreting clinician.

Many factors influence the overall interpretability of an AI system, but the complexity of the underlying model is a key determinant. Some AI algorithms, such as decision trees, are

easy to understand and have predictable deterministic performance, while artificial neural networks can have up to 175 billion parameters [180] which obfuscates their interpretation. Even simple decision trees lack interpretability when they are used as part of ensemble learning, where many decision trees are combined to form stochastic algorithms such as random forests or gradient-boosted trees [181]. In such cases additional aids, post-hoc analysis, or surrogate models can sometimes explain the AI system's results [9]. Feature importance scoring, using methods such as SHAPely additive explanation [182], is another approach that may increase system interpretability.

A model that reports the uncertainty associated with each prediction aids the usability of an algorithm, without necessarily improving interpretability and transparency. If a set of possible outcomes and their associated probabilities are presented, rather than a single dichotomous classification, then clinicians can integrate this information into their clinical decision-making [183].

8.3. Explainability

Many authors state that transparency for a medical AI system that uses a neural network (deep learning) needs to include the ability of the user to understand the structure of the network and the features that it has identified; interpretability then refers to the ability to understand the inner mechanics of the model. For example, if 'the associations between the individual features and the outcome remain hidden, the predictions are difficult to scrutinize and to question [...] underlining the importance of explicability, also to avoid incorrectly inferring that the strongest associations between features and outcome indicate causal relations' [184].

There is a contrary view that the benefits of understanding the detailed internal operation of a neural network are overrated [185]. Even if a 'black box' is impenetrable, the performance of an algorithm can always be understood and interpreted at a higher level; 'rather than seeking explanations for each behaviour of a computer system, policies should formalize and make known the assumptions, choices, and adequacy determinations associated with a system' [186]. Markus and colleagues provide a useful summary of the components of explainability and interpretability [187]. These authors suggest that for clinical applications, criteria such as the quality of the input data, the robustness or reproducibility of the algorithm, and the results of external validation, are more important. Explainability would then be defined as the ability to explain the behavior of an ML model in human terms.

8.4. Implications for regulatory guidance

There is considerable heterogeneity between AI models even within the same class of algorithm, and providing a taxonomy of AI methods linked to their regulatory implications would be challenging. Nonetheless within each category of ML algorithms, it may be helpful to understand which methods are more or less transparent since those criteria will impact on how the evidence is assessed. Many gradings of software are qualitative and subjective, but a pragmatic approach could provide a summary of simple criteria of AI systems that notified bodies and regulators can assess.

9. Conclusions

Medical devices incorporating AI are being deployed rapidly and are already widely used. On 5 October 2022 the FDA listed 521 AI-enabled medical devices that it has approved since 1997 [188]. Regulatory guidance needs to keep pace with this fast progress and with technological developments. It would make sense for regulatory efforts to be concentrated on gaps in advice [36] or on challenges that are unique to AI devices, such as how to assure that software is applied only in the circumstances for which and for individuals in whom its use has been validated, how to cope with the need for approval of iterative changes in software that may be self-learning, and how to conduct appropriate post-market surveillance. Special provisions for AI-related aspects of each class of medical devices would best be an integral part of their overall evaluation requirements, ideally described in harmonized standards or, when lacking, common specifications. The primary focus should always be on the purpose of the AI rather than the technology.

10. Expert opinion

We have identified considerable concordance between recommendations about AI, and a remarkable plethora of stakeholders involved in developing guidance and regulations (Figure 3). Their varying constitutions, authority, responsibilities and acronyms (such as FG-AI4H, C4AI, WP AIGO, GPAI, CAI, and SRAHG; all explained in this review) have become confusing and their collective but apparently uncoordinated engagement is probably counterproductive. There are likely to be other and more recent initiatives of which we are unaware. Unless they are all coordinated, there is a real risk of over-regulation.

Principle 2.5 from the OECD, on international cooperation for trustworthy AI, states that 'Governments should promote the development of multi-stakeholder, consensus-driven global technical standards for interoperable and trustworthy AI.' A report from the Council of Europe says that 'robust testing and validation standards should be an essential predeployment requirement for AI systems in clinical care contexts' [109]. Many other organizations reached similar conclusions. We would add that for medical AI systems as for all high-risk medical devices, standards should be based on scientific evidence and proportionate to the clinical risks. Within the EU there should be collaboration between medical device regulators and EMA, and at the international level there should be collaboration between IMDRF and ICMRA. A concrete and practical initiative for global regulatory convergence would be sensible.

10.1. Concordance needed for scope of definitions

Precise regulatory definitions of what qualifies as an AI system that will need approval as a medical device vary between jurisdictions. In the USA, the FDA does not consider

Figure 3. Overview of European and global institutions and organizations engaged in the development of regulations for medical AI systems.
Details of all these acronyms are given in the text.
The logo in the top left corner is the symbol for the CORE-MD consortium.

software that has the purpose (only) to 'inform' to be a medical device, if the software is used by a healthcare professional who is expected to be able to review the evidence underlying the information, independently [189]. Similarly, Australian regulations exclude clinical decision support software with limited functions that does not replace the judgment of a healthcare professional [190]. The scope of FDA regulations on SaMD and ML has been further narrowed by excluding software that does not receive, analyze or otherwise process a medical image or signal from a medical device or an *in vitro* diagnostic medical device or from any other signal acquisition system, and by specifying that a healthcare professional must be able to understand the basis of its recommendations (but not necessarily the exact processes) [191].

All low-risk software that used to be class I was deregulated under the US 21st Century Cures Act of 2016 [192]. In the EU, software with a search function does not qualify [5] but AI algorithms that calculate a prognostic score are designated as medical devices. Logistic regression software for routine checkups by healthcare professionals does not qualify as SaMD in the USA, while it can be considered as MDSW in the EU. Concordance of scope and regulatory requirements would be preferable.

10.2. Rationale for standards

The personal risks arising from autonomous systems that employ AI for non-medical applications appear greater than occur currently with the vast majority of AI applications in healthcare, and thus they indeed merit public safeguards as envisaged by the EU AI Act. Specific standards for AI medical devices, however, should be determined by their particular clinical risks. That has been the focus of the IMDRF documents, and more recently of the ICMRA report since it concurred that

'regulators may need to apply a risk-based approach to assessing and regulating AI' [128]. Standards for assessing AI as a medical device should consider both the components of the system and the context in which it is deployed [193]. The need for transparency as the foundation for evidence-based clinical practice extends to the standards applied for AI devices. European harmonized standards undergo public consultation, but it is unsatisfactory that ISO and IEC standards are developed without open public consultation and available only for purchase.

Concepts have become clouded by the inappropriate use of anthropomorphic language to describe functions of AI algorithms that their developers and users have determined, and by the tendency to refer to 'AI' as a single technology. AI tools do not replicate the thought processes employed by clinicians in practice [194] so it might be wiser to refer to human intelligence *augmented* by computer algorithmic tools. Current vocabulary leads to the idea that AI somehow is different – but the basic principles for its regulation in healthcare are not. All high-risk medical devices should be evaluated to establish evidence of clinical benefit and minimal risk before they are approved. It is noteworthy that the fields that are common to all the professional recommendations (see Table 6: data acquisition, preprocessing, model, study population, performance, benchmarking, and data availability) are relevant not only for studies of AI medical devices but also for all clinical research studies and statistical analyses.

10.3. Determinants of risk for classifying software

Expert review by scientists and clinicians would clarify which AI systems should be regarded as high-risk (class IIb or class III) medical devices, and which methodologies would then be indicated for clinical evaluation to demonstrate their scientific

validity. The CORE-MD project will consider those questions and prepare recommendations separately, taking note of relevant questions that have been suggested or are being prepared by other authors [36,76,195–197]. Although it has not been a focus of this review, similar considerations would apply to the designation of *in vitro* diagnostic medical devices (IVDs) that use AI, either as Class C or Class D [198].

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Declarations of interest

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