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A unifying force for the realization of medical AI

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Artificial Intelligence (AI) in medicine has grown rapidly, yet few algorithms have been deployed. It is not the problem with the AI itself but with the way functions and results are communicated. Regulatory science provides the appropriate language and solutions to this problem for three reasons: First, there is value in the intentionally interdisciplinary regulatory language. Second, regulatory concepts are important for AI researchers because these concepts enable tackling of risk and safety concerns as well as understanding of recently proposed regulations in the US and Europe. Third, regulatory science is a scientific discipline that evaluates and challenges current regulation—aiming for evidence-based improvements. Knowledge of the regulatory language, concepts, and science should be regarded a core competency for communicating medical innovation. Regulatory grade communication will be the key to bringing medical AI from hype to standard of care. Foregoing the possible benefits of regulatory science as a unifying force for the realization of medical AI is a missed opportunity.

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The past few years has seen a rapid growth of AI in medicine, however, few algorithms have been deployed in clinical practice[1]. We view this disconnect between hype and reality as stemming from two main barriers: first, the lack of a common language between AI and medicine, and second, the rapid progress in AI outpacing the comparatively slow adaptation of regulation, forcing regulatory bodies to apply measures that do not always consider the paradigm-shifting capabilities of contemporary AI. We propose regulatory science with its terms and concepts as a solution for both problems because it represents a high-level language that can serve as a unifying force for the realization of medical AI (Fig. 1).

Regulatory science is the scientific discipline that *evaluates* and *challenges* current regulation, benefit vs. risk assessments, and submission/approval strategies[2]. It is the application of the scientific method to enable evidence-based improvements of regulation, and just as new scientific evidence can be powerful enough to change the paradigm of a field of study, so too can it change regulatory paradigms.

Fundamentally, regulatory science is about creating a dialogue for launching new ideas and determining how best to allow those ideas to interact with society-not only from within regulatory authorities but also through collaborations between academics, clinicians, industry, payors, policy experts, and patients. Like any scientific discipline, regulatory science comes with a specific language, but given its core translational nature, its language is intentionally interdisciplinary to enable deep collaborations. The terms and concepts traverse specific use cases and provide a contextual vocabulary that enables clear communication beyond use case of medical subspecialty (Supplementary Table 1). In other words, regulatory language is unifying.

For example, one challenge we have personally encountered (and have witnessed frequently among others) is clearly communicating the specific task of medical AI in a way that is mutually intelligible for medical and AI experts. Medical education opens one's eyes to the enormously complex systems that have evolved for treating patients through our incomplete understanding of biology. The inherent subjectivity and guesswork in medicine can be appalling to AI experts more used to dealing with systems that are, at least in theory, rationally designed and better understood. Given the interconnectedness and subjectivity inherent in essentially all interactions a patient has with the healthcare system, defining the boundaries of a problem where AI could provide a solution becomes an issue in and of itself. For example, subtle changes in diagnosis can lead to huge changes in management. These subtleties are accounted for in the evolving and continuously updated definitions that make up the language of regulatory science. Terminology from regulatory science such as *intended use* ("what"), *indication of use* ("who and why"), or *instructions for use* ("how"); can help both sides communicate precisely about the scope of the problem at hand and how to center the patient in this discussion (Fig. 2).

Centering benefit to the patient is the goal of effective regulation, but the prevailing regulatory paradigms have not been optimized for AI in medicine. By and large, they have been adapted through continuous iteration to best review and approve drugs, medical devices, or software (as a medical device) that is fundamentally different from AI—especially when algorithms continuously evolve. A burgeoning body of research has shown that AI algorithms can fail in non-trivial ways, from poor generalization due to dataset shift, to overfitting to confounders, to unexpected failure modes[3].

These challenges must be addressed before AI can be used safely in clinical practice. Thankfully, similar barriers have been overcome in other domains of medicine and their solutions codified into regulation. For example, there is a growing recognition that ongoing performance assessment of a deployed AI model is key to combating dataset shift, a concept that follows the principles of continued monitoring of post-market surveillance required by the FDA. There are numerous regulatory resources (Supplementary Table 1)[4] to address software, medical AI, and change modifications[5–8]. Much additional work is needed though, with the prevailing FDA regulations (Supplementary Table 1) or ISO governance approaches (Supplementary Table 2) dispersed across over 25 guidance[2] or standard documents, respectively.

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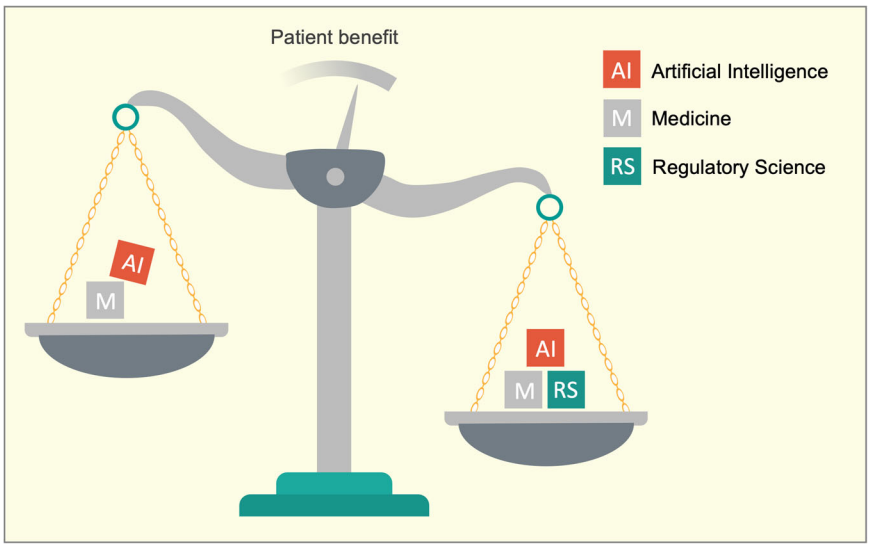

Fig. 1 Regulatory science and AI in medicine. The application of AI in medicine aims to benefit patients. The disciplines of artificial intelligence (AI; a branch of computer science) and medicine are coexisting without a shared interdisciplinary language that enables expedient risk and benefit assessments. Regulatory science is characterized by specific and intentionally interdisciplinary language that considers multiple vantage points. Regulatory science is one proven approach to use scientific data to evaluate and challenge current regulatory paradigms and inform future regulation.

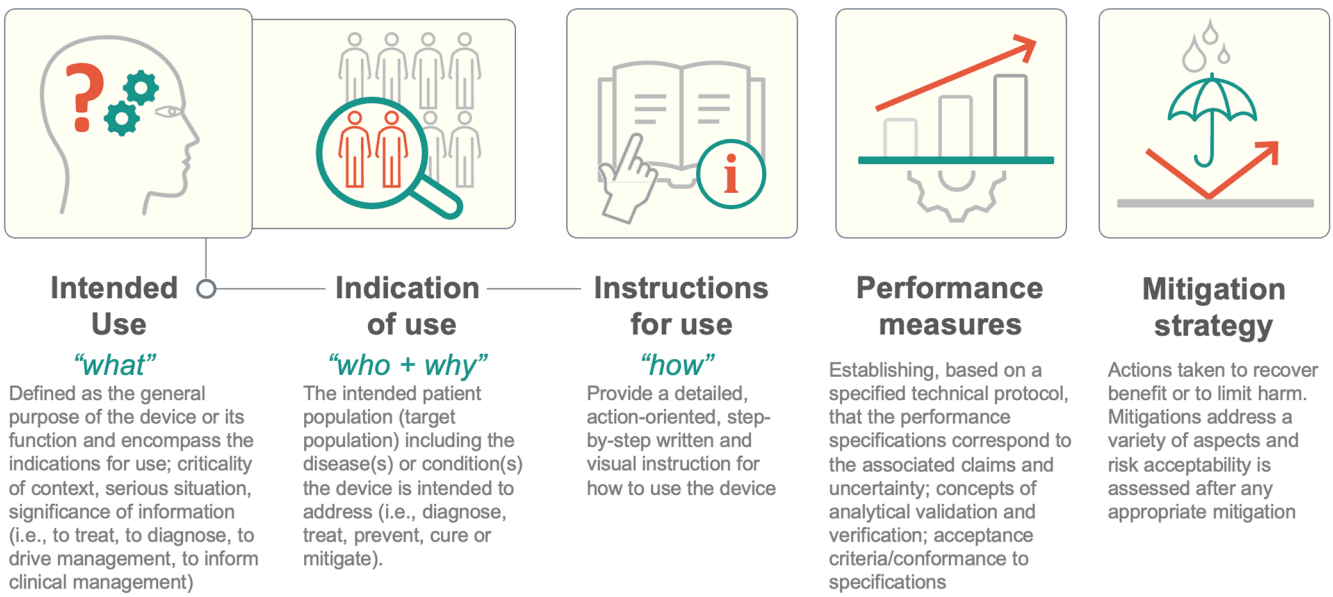

Fig. 2 Selected regulatory science concepts. The infographic depicts 5 regulatory concepts alongside a brief explanation. Detailing these aspects provides a reasonable starting point to describe the function of a medical AI algorithm and the value of regulatory concepts for streamlining interdisciplinary communication.

One key question is whether applying regulatory paradigms can supplement the more traditional strength/weaknesses approach pursued in research. We have reconstructed examples where the addition or regulatory principles resulted in documented improvements (Supplementary Table 3). Briefly, the *IBM Watson Content Analytics* had a poorly described *intended use*; however, subsequent publications clearly communicate value propositions in regulatory terms (Supplementary Table 3). Google's AI-screening for diabetic retinopathy is an example where the lack of *instructions for use* was responsible for key performance issues (e.g., operating the device in a dark room). Notably, the lack of regulatory aspects was in direct contradiction to simultaneously published regulatory comments from the FDA and (notably) google itself—emphasizing the importance of regulatory consistencies (Supplementary Table 3). In other words, we can reconstruct that two of the most drastic AI fiascoes entailed inconsistencies in communication that resulted in miscommunication between AI and healthcare experts. Other examples include documented improvements in objectivity and reproducibility when tailoring performance measures to the specific *target population*. Notably, adoption of the algorithm based on the *target population*-matched (as a *mitigation strategy*) enabled overcoming a biomarker challenge in ovarian cancer screening previously flagged as a public health concern (Supplementary Table 3). These examples illustrate that regulatory concepts are consequential and hold clinical value beyond a vantage point in a research publication.

The unique strengths and weaknesses of AI require new regulation to be developed and old regulation to be altered. For example, US-based regulatory guidances and the European Artificial Intelligence Act[9] already account for regulatory compliant reporting of change protocols (Supplementary Table 1), a change that accounts for potential problems identified during and after deployment of continuously learning AI models. These guidance and legislative axioms argue strongly for a role of regulatory terminology as one of the key factors impacting the integration of AI approaches in medicine. Learning the language of regulatory science also confronts us with the fact that regulation, rather than being handed down from on high, is a human endeavor; that regulations are made by people who are reviewing the data and input that AI and medical experts generate, and that regulation can (and should) be challenged and updated. In the US, the FDA established several strategies to address regulatory challenges by obtaining external, interdisciplinary input (Supplementary Table 4). These programs offer concrete and practical approaches to incorporate inputs from the technical communities. For example, the FDA engages with outside experts via collaborative communities, a network of experts, and specific medical device development tool programs, to keep up with changes in the fields under its purview. Concretely, these initiatives have already influenced recent legislative proposals that now clearly spell out the need for "recommendations and other advice" from domain-experts to facilitate meaningful regulatory guidance[10]. Learning the language of regulatory science can help those who know the most about medical AI to effectively influence the nascent regulatory landscape.

We view regulatory science as a fundamental building block of healthcare that now also focusses on using AI to improve patients' lives. Regulatory science, its language and concepts have the potential to facilitate communication and collaboration between the fields of AI and medicine, as well as between the broader medical AI community and regulatory bodies. Knowledge of the regulatory language, concepts, and science should be regarded a core competency for communicating medical innovation. Regulatory grade communication will be the key to bringing medical AI from hype to standard of care.

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AUTHOR CONTRIBUTIONS

J.K.L. and F.M. wrote an initial draft; U.G. and D.K.F.W. revised the initial draft; U.G., D.F.K.W., and J.K.L. conceptualized the figures; all authors approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Supplementary Information

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Supplementary Tables

Supplementary Table 1. Selected Regulatory Science Concepts Relevant to Artificial Intelligence and Software as a Medical Device

Concept	Abbreviated Explanation	Reference
General Principles	General Principles of Software Validation	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-principles-software-validation https://www.regulations.gov/docket/FDA-1997-D-0029
Substantial equivalence	The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]	Link to guidance
Benefit Risk Assessments	Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-regarding-benefit-risk-medical-device-product-availability-compliance-and
Instructions for use (IFU)	IFU should contain detailed, action-oriented, step-by-step written and visual instructions provide	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/instructions-use-patient-labeling-human-prescription-drug-and-biological-products-content-and-format
CDRH Labeling Regulatory Requirements for Medical Devices	The U.S. Food and Drug Administration (FDA) develops and administers regulations under authority granted by laws passed by Congress that apply to food, drugs, cosmetics, biologics, radiation-emitting electronic products, and medical devices. Labeling regulations pertaining to medical devices are found in the following Parts of Title 21 of the Code of Federal Regulations (CFR).	https://www.fda.gov/medical-devices/overview-device-regulation/device-labeling
	Older but highly informative guidance document	https://www.fda.gov/media/74034/download
	Device Labeling	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-medical-device-patient-labeling
Medical Device Labeling	General Device Labeling	21 CFR Part 801
	Use of Symbols	21 CFR Part 801.15
	In Vitro Diagnostic Products	21 CFR Part 809
	Investigational Device Exemptions	21 CFR Part 812
	Unique Device Identification	21CFR Part 830
	Good Manufacturing Practices	21 CFR Part 820
	General Electronic Products	21 CFR Part 1010
Performance Assessment (example)	Technical Performance Assessment of Quantitative Imaging in Radiological Device Premarket Submissions	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-performance-assessment-quantitative-imaging-radiological-device-premarket-submissions
Definition of label	Section 201(k)	https://www.fda.gov/medical-devices/overview-device-regulation/device-labeling
Medical Devices Technical Corrections Act (MDTCA)	Corrections and explanations	www.fda.gov/cdrh/mdufma/hrpt108-433.pdf
Off-the Shelf Software	OTS Software in a medical device allows the manufacturer to concentrate on the application software needed to run device-specific functions. OTS Software intended for general-purpose computing may not be appropriate for a given specific use in a medical device. The medical device manufacturer using OTS Software generally gives up software life cycle control, but still bears the responsibility for the continued safe and effective performance of the medical device.	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/shelf-software-use-medical-devices https://www.regulations.gov/docket/FDA-2019-D-3598
Software Consensus Standards	Database provides the most up-to-date list of voluntary consensus standards to which FDA will accept a Declaration of Conformity	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm e.g., ISO 14971; AAMI SW68; DICOM https://www.dicomstandard.org/
Quality System Regulation	requirements for the establishment and maintenance of a quality management system	21 CFRpart820; ISO 13485:2016; https://www.fda.gov/medical-devices/postmarket-requirements-devices/quality-system-qs-regulationmedical-device-good-manufacturing-practices
Verification	Defined as means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled. Walk-throughs, Various static and dynamic analyses, Code and document inspections, Module and level testing, Integration testing. Documentation	21CFR820.3(aa)
Validation / Design Validation	Defined as means establishing by objective evidence that device specifications (here software) conform with user needs and intended use(s). Planning, verification, traceability, configuration management, and many other aspects of good software engineering. Documentation	21 CFR 820.3(z)(2)
Process Validation	Process Validation is defined as the. collection and evaluation of data, from the. process design stage throughout. production, which establishes scientific evidence that a process is capable of consistently delivering quality products.	21 CFR 820.3(z)(1)
The Least Burdensome Approach	Defined as the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time	Link to guidance document
Injuries / Serious Injuries	Definition of a serious injury is life threatening, or results in permanent impairment of a body function or permanent damage to a body structure; or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.	21CFR803.3(bb)(1) and (2)
Level of Concern (Minor, Moderate, Major)	Level of Concern should be driven by the hazard analysis in the absence of mitigations, regardless of the effects of the mitigations on the individual hazards. Major if a failure or latent flaw could directly result in death or serious injury to the patient or operator. Moderate if a failure or latent design flaw could directly result in minor injury to the patient or operator. Minor if failures or latent design flaws are unlikely to cause any injury to the patient or operator.	https://www.regulations.gov/docket/FDA-2020-D-0957
Documentation	device-specific guidance; design description of the device, documentation of how the design was implemented, demonstrate design implementation testing, identified hazards and managed risks, traceability to link design, implementation, testing, and risk management	https://www.regulations.gov/docket/FDA-2020-D-0957
Software Description	comprehensive overview of the device features that are controlled by software, and describe the intended operational environment : programming language, hardware platform, operating system (if applicable), use of Off-the-Shelf software (if applicable)	https://www.regulations.gov/docket/FDA-2020-D-0957
Device Hazard Analysis / Risk Management Summary	Identification of the hazardous event, severity of the hazard, cause(s) of the hazard, method of control (e.g., alarm, hardware design), corrective measures taken (including an explanation of the aspects of the device deisng/requirments that eliminate, reduce, or warn of a hazardouse event), and verification that the method of control was implemented correctly	ISO 14971
Software Requirements Specification (SRS)	Hardware Requirements, Programming Language Requirements, Interface Requirements, Software Performance and Functional Requirements	https://www.regulations.gov/docket/FDA-2020-D-0957
Revision Level History	History of software revisions	https://www.regulations.gov/docket/FDA-2020-D-0957
Unresolved Anomalies (Bugs or Defects)	Problem, Impact on device performance, any plans or timeframes for correcting the problem (where appropriate)	https://www.regulations.gov/docket/FDA-2020-D-0957
Software Change Management	Design, development, testing, and version control of revisions to the software	https://www.regulations.gov/docket/FDA-2020-D-0957 https://www.regulations.gov/docket/FDA-2016-D-2021 https://www.regulations.gov/docket/FDA-2016-D-2021
Change Management Biological Product	Changes to an Approved Application: Biological Products	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-application-biological-products
Change Management NDA/ANDA	Changes to an Approved NDA or ANDA	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-nda-or-anda
Software of Unknown Pedigree (SOUP)	Software contained in a Software Device may have been obtained by the submitter from a third party	https://en.wikipedia.org/wiki/Software_of_unknown_pedigree https://en.wikipedia.org/wiki/IEC_62304
Combined Products	Drug-device and biologics-device combinations	https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products
Virus Protection Software	Antivirus products work by detecting, quarantining and/or deleting malicious code, to prevent malware from causing damage to your device. Modern antivirus products update themselves automatically, to provide protection against the latest viruses and other types of malware.	https://www.fda.gov/medical-devices/digital-health-center-excellence/cybersecurity
Interfaces, Networking, and Network Infrastructure	Network infrastructure is the hardware and software that enables network connectivity and communication between users, devices, apps, and the internet.	https://www.fda.gov/files/about%20fda/published/Modernization_in_Action_2022.pdf
Architecture Design Chart	An architectural diagram is a visual representation that maps out the physical implementation for components of a software system. It shows the general structure of the software system and the associations, limitations, and boundaries between each element.	https://www.regulations.gov/docket/FDA-2020-D-0957
Software Design Specification	A software design document—sometimes called software design specification—is a detailed plan for developing a piece of software. An SDD should outline the finished software's functionality (specs) and your team's plans to build it (timeline, goals, etc.).	https://www.regulations.gov/docket/FDA-2020-D-0957
Traceability Analysis	The analysis of the relationships between two or more products of the development process conducted to determine that objectives have been met or that the effort represented by the products is completed.	https://www.regulations.gov/docket/FDA-2020-D-0957
Software Development Environment Description	the development environment is a workspace with a set of processes and programming tools used to develop the source code for an application or software product.	https://www.regulations.gov/docket/FDA-2020-D-0957
Submission Content	Content of Premarket Submissions for Device Software Functions	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-device-software-functions
Breakthrough designation	The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.	https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program#s1
Acceptance criteria/Specification	A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described.	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q6b-specifications-test-procedures-and-acceptance-criteria-biotechnologicalbiological-products
Conformance to specifications	Conformance to specification menas that when a device is tested according to the listed analytical procedures, will meet the acceptance criteria.	https://www.fda.gov/medical-devices/premarket-notification-510k/acceptance-checklists-510ks
Software as a Medical Device (SaMD)	Software, which on its own is a medical device – Software as a Medical Device – is one of three types of software related to medical devices.	https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd https://pubmed.ncbi.nlm.nih.gov/31818387/
Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices	As technology continues to advance every aspect of health care, software incorporating artificial intelligence (AI), and specifically the subset of AI known as machine learning (ML), has become an important part of an increasing number of medical devices.	https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices

Supplementary Table 2. Selected ISO Governance Approaches for Regulating Artifical Intelligence

WORKING GROUPS	
ISO/IEC JTC 1/SC 42/AG 3	AI standardization roadmapping
ISO/IEC JTC 1/SC 42/AHG 1	Dissemination and outreach
ISO/IEC JTC 1/SC 42/AHG 2	Liaison with SC 38
ISO/IEC JTC 1/SC 42/AHG 4	Liaison with SC 27
ISO/IEC JTC 1/SC 42/AHG 5	AI standardization landscape and roadmap
ISO/IEC JTC 1/SC 42/JWG 1	Joint Working Group ISO/IEC JTC1/SC 42 - ISO/IEC JTC1/SC 40: Governance implications of AI
ISO/IEC JTC 1/SC 42/JWG 2	Joint Working Group ISO/IEC JTC1/SC 42 - ISO/IEC JTC1/SC 7 : Testing of AI-based systems
ISO/IEC JTC 1/SC 42/WG 1	Foundational standards
ISO/IEC JTC 1/SC 42/WG 2	Data
ISO/IEC JTC 1/SC 42/WG 3	Trustworthiness
ISO/IEC JTC 1/SC 42/WG 4	Use cases and applications
ISO/IEC JTC 1/SC 42/WG 5	Computational approaches and computational characteristics of AI systems

STANDARD AND/OR PROJECT	
ISO/IEC DTS 4213.2	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 AWI 5339	Information Technology — Artificial Intelligence — Guidelines for AI applications
ISO/IEC AWI 5392	Information technology — Artificial intelligence — Reference architecture of knowledge engineering
ISO/IEC AWI TR 5469	Artificial intelligence — Functional safety and AI systems
ISO/IEC AWI TS 5471	Artificial intelligence — Quality evaluation guidelines for AI systems
ISO/IEC AWI TS 6254	Information technology — Artificial intelligence — Objectives and approaches for explainability of ML models and AI systems
ISO/IEC CD 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 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 FDIS 22989	Information technology — Artificial intelligence — Artificial intelligence concepts and terminology
ISO/IEC FDIS 23053	Framework for Artificial Intelligence (AI) Systems Using Machine Learning (ML)
ISO/IEC DIS 23894	Information technology — Artificial intelligence — Risk management
ISO/IEC CD 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 DTR 24368	Information technology — Artificial intelligence — Overview of ethical and societal concerns
ISO/IEC DIS 24668	Information technology — Artificial intelligence — Process management framework for big data analytics
ISO/IEC CD 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 FDIS 38507	Information technology — Governance of IT — Governance implications of the use of artificial intelligence by organizations
ISO/IEC CD 42001	Information Technology — Artificial intelligence — Management system

Supplementary Table 3. Examples of AI-tools where the Addition of Regulatory Language and/or Concepts Resulted in Documented Improvements

No.	Publication	Promise, purpose, or quote	Source	Regulatory Concept	Disconnect	Evidence for Improvement by using Regulatory Science Terms	Source
1	**IBM Watson** wiki	• "*AI-assisted screening process*" for Diabetic Retinopathy (REF) (April 2020)	ibm.com/redbook	• Intended use	• Intended use was poorly described	• Subsequent publications and strategy emphasize regulatory aspects • Clarification of functionality	Conceptual Modeling PMID: 34920529
		• "*Currently, there are no requirements for AI systems to be evaluated through observational clinical studies, nor is it common practice*"	ibm.com/redbook			• IBM authors acknowledge critical role of regulatory aspects	PMID: 33463680
						• IBM joins ÉCLAIR guidelines, prominently feature regultory aspects	PMID: 33666696
2	**Google** CHI paper	• "*AI-assisted screening process*" for Diabetic Retinopathy (April 2020)	CHI paper	• Instructions for use	• Software as a Medical Device (SaMD) guidance (Dec 2018)	• Appropriate instructions for use can prevent some of the published mishaps	Recommendations
		• "*Currently, there are no requirements for AI systems to be evaluated through observational clinical studies, nor is it common practice*"	CHI paper		• Miscommunication between computer science and regulatory team • European approach	• Concurrent google publication emphasize importance of regulatory aspects (May 2020) • Recognition of 'context of use'	Recommendations Public comment
3	**ROC curve** Use and Misuse	• AI tool to predict reportability of genetic variants	Publication	• Indication of use (performance measures)	• Follow established statistical guidance	• "…Improvements to objectivity and reproducibility…"	PMID: 34979564
		• Performance reporting using ROC curve	Use and Misuse		• Statistical guidance exists but is not followed	• "…biases may exist in our model with regard to (…) the ethnicity or ancestry of our testing	PMID: 30364844
4	**FDA 20 case studies** Evidence	• Algorithmic analysis for ovarian cancer screening	Evidence	• Performance measures	• Follow established statistical guidance	• FDA authorized test available	Decision summary
			PMID: 12795817			• "Software algorithm that combines five immunoassays into a single score"	Decision summary
				• Indication of use (Target population)	• Not reported (i.e., proprietary) PMID: 14996856	• One equation with 2 cut-offs by menopausal status	Decision summary
				• Mitigation strategy	• Not included	• Should not be used without an independent clinical and imaging evaluation	Decision summary

Supplementary Table 4. Established Interdisciplinary Strategies to Address Regulatory Challenges

Aspect	Approach	Reference/Source
Review Teams	The FDA and EMA review teams involve team members from different disciplines working collaboratively, with a common purpose, to set goals, make decisions and share resources and responsibilities.	https://www.fda.gov/industry/fda-basics-industry/guidances
		https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/class-ii-special-controls-documents
		https://www.ema.europa.eu/en/committees/how-committees-work
Guidance creation	The creation of a guidance document follows very specific paradigms that entails multiple steps that go beyond the input from immediate subject matter experts. For example, there is an intricate intra-agency review and approval process. Furthermore, the guidance document is released as a draft guidance with a public commenting period.	Link to FDA SOP
Research by the regulators		
	The FDA performs scientific research (e.g., Office of Science and Engineering Laboratories)	https://www.fda.gov/about-fda/cdrh-offices/office-science-and-engineering-laboratories
Example NCTR	**National Center for Toxicological Research; Focus Areas**	https://www.fda.gov/about-fda/science-research-nctr/nctr-research-focus-areas
	Artificial Intelligence	https://www.fda.gov/about-fda/nctr-research-focus-areas/artificial-intelligence
	Systems Biology	https://www.fda.gov/about-fda/nctr-research-offices-and-divisions/nctr-division-systems-biology
	Bio-Imaging	https://www.fda.gov/about-fda/nctr-research-focus-areas/bio-imaging
	Nanotechnology	https://www.fda.gov/about-fda/nctr-research-focus-areas/bio-imaging
	Perinatal and Maternal Research at NCTR	https://www.fda.gov/about-fda/nctr-research-focus-areas/perinatal-and-maternal-research
	Personalized Medicine	https://www.fda.gov/about-fda/nctr-research-offices-and-divisions/nctr-division-systems-biology
	NCTR bioinformatics tools	https://www.fda.gov/science-research/bioinformatics-tools
	Regulatory Science Training	https://www.fda.gov/about-fda/nctr-research-focus-areas/regulatory-science-training
	Faculty Research Program (NCTR)	https://www.fda.gov/about-fda/scientific-internships-fellowships-trainees-and-non-us-citizens/faculty-research-program-nctr
	Foregin National Training Program (NCTR)	https://www.fda.gov/about-fda/scientific-internships-fellowships-trainees-and-non-us-citizens/foreign-national-training-program-nctr
	Interdisciplinary Toxicology Program	https://www.fda.gov/about-fda/scientific-internships-fellowships-trainees-and-non-us-citizens/interdisciplinary-toxicology-program
	Postgraduate Research Program (NCTR)	https://www.fda.gov/about-fda/scientific-internships-fellowships-trainees-and-non-us-citizens/postgraduate-research-program-nctr
	Science Internship Program (NCTR)	https://www.fda.gov/about-fda/scientific-internships-fellowships-trainees-and-non-us-citizens/science-internship-program-nctr
	Summer Student Research Program (NCTR)	https://www.fda.gov/about-fda/scientific-internships-fellowships-trainees-and-non-us-citizens/summer-student-research-program-nctr
	Graduate Certificate in Regulatory Science	https://publichealth.uams.edu/academics/certificates/certificate-in-regulatory-science/
Example OSEL	The Office of Science and Engineering Laboratories (OSEL) is composed of scientists and engineers who have a broad diversity of expertise from microbiology to artificial intelligence and machine learning. We are all dedicated to promoting innovation for the development of new lifesaving medical devices.	https://www.fda.gov/about-fda/cdrh-offices/office-science-and-engineering-laboratories
	Additive Manufacturing	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/additive-manufacturing-program-research-additive-manufacturing-medical-devices
	Artificial Intelligence and Machine Learning (AI/ML)	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/artificial-intelligence-and-machine-learning-program-research-aiml-based-medical-devices
	Biocompatibility and Toxicology	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/biocompatibility-and-toxicology-program-research-medical-devices-biocompatibility-and-toxicology
	Cardiovascular	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/cardiovascular-program-research-cardiovascular-medical-devices
	Credibility of Computational Models	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/credibility-computational-models-program-research-computational-models-and-simulation-associated
	Digital Pathology	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/digital-pathology-program-research-digital-pathology-medical-devices
	Electromagnetic and Electrical Safety	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/electromagnetic-and-electrical-safety-program-research-electromagnetic-and-electrical-safety-medical
	Emergency Preparedness	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/emergency-preparedness-program-research-medical-devices-emergencies
	Human Device Interaction	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/human-device-interaction-program-research-human-interaction-medical-devices
	Materials Performance	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/materials-performance-program-research-materials-performance-medical-devices
	Medical Extended Reality	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/medical-extended-reality-program-research-medical-extended-reality-based-medical-devices
	Medical Imaging and Diagnostics	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/medical-imaging-and-diagnostics-program-research-medical-imaging-and-diagnostic-devices
	Microbiology and Infection Control	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/microbiology-and-infection-control-program-research-microbial-and-infection-control-medical-devices
	Microfluidics	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/microfluidics-program-research-microfluidics-based-medical-devices
	Neurology	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/neurology-program-research-neurology-medical-devices
	Ophthalmology	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/ophthalmology-program-research-ophthalmology-medical-devices
	Orthopedic Devices	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/orthopedic-devices-program-research-orthopedic-medical-devices
	Patient Monitoring and Control	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/patient-monitoring-and-control-program-research-patient-monitoring-and-control-devices
	Therapeutic Ultrasound	https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/therapeutic-ultrasound-program-research-therapeutic-ultrasound-medical-devices
	OSEL Divisions	https://www.fda.gov/about-fda/cdrh-offices/office-science-and-engineering-laboratories
	Division of Applied Mechanics (DAM)	https://www.fda.gov/about-fda/cdrh-offices/division-applied-mechanics
	Division of Biomedical Physics (DBP)	https://www.fda.gov/about-fda/cdrh-offices/division-biomedical-physics
	Division of Biology, Chemistry, and Materials Science (DBCMS)	https://www.fda.gov/about-fda/cdrh-offices/division-biology-chemistry-and-materials-science
	Division of Imaging, Diagnostics, and Software Reliability (DIDSR)	https://www.fda.gov/about-fda/cdrh-offices/division-imaging-diagnostics-and-software-reliability
Example ARHQ	The Agency for Healthcare Research and Quality's (AHRQ) mission is to produce evidence to make health care safer, higher quality, more accessible, equitable, and affordable, and to work within the U.S. Department of Health and Human Services and with other partners to make sure that the evidence is understood and used. We accomplish our mission by focusing on our three core competencies.	https://www.ahrq.gov/
Regulatory Resources		
	Guidance database	https://www.fda.gov/regulatory-information/search-fda-guidance-documents
	Artificial Intelligence and Machine Learning (AI/ML) Software as a Medical Device Action Plan	https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device
	Artificial Intelligence and Machine Learning (AI/ML)-Enable Medical Devices	https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices
	Deciding When to Submit a 510(k) for a Software Change to an Existing Device	Link to guidance
	An FDA Artificial Intelligence (AI) Program for Toxicology at NCTR	https://www.fda.gov/about-fda/nctr-research-focus-areas/artificial-intelligence
	AnimalGAN	https://www.fda.gov/about-fda/nctr-research-focus-areas/animalgan-initiative
	SafetAI	https://www.fda.gov/about-fda/nctr-research-focus-areas/safetai-initiative
	BERTox	https://www.fda.gov/about-fda/nctr-research-focus-areas/bertox-initiative
	PathologAI	https://www.fda.gov/about-fda/nctr-research-focus-areas/pathologai-initiative
	Medical Device Databases	https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/medical-device-databases
	FDA product code classification database	https://www.fda.gov/medical-devices/classify-your-medical-device/product-code-classification-database
	Catalogue of Regulatory Science Tools	https://www.fda.gov/medical-devices/science-and-research-medical-devices/catalog-regulatory-science-tools-help-assess-new-medical-devices
	Multi-Reader, Multi-Case Analysis Methods (iMRMC)	https://cran.r-project.org/web/packages/iMRMC/index.html
	Software as a Medical Device (SaMD)	https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd
	Structured Product Labeling Commercial Software and Conversion Vendors and FDA-Regulated Company Self-Generated SPL Software	https://www.fda.gov/industry/fda-data-standards-advisory-board/structured-product-labeling-resources
	Device Software Functions Including Mobile Medical Applications	https://www.fda.gov/medical-devices/digital-health-center-excellence/device-software-functions-including-mobile-medical-applications
	Medicines and Healthcare Products Regulatory Agency (MHRA), software flow chart	Link to flowchart
Programs and Initiatves (Selection)		
	The Medical Device Development Tool (MDDT) program	https://www.fda.gov/medical-devices/medical-device-development-tools-mddt
	Network of Expert (NoE)	https://www.fda.gov/about-fda/center-devices-and-radiological-health/network-experts-program-connecting-fda-external-expertise
	Digital Health Center of Excellence (DHCoE)	https://www.fda.gov/medical-devices/digital-health-center-excellence
	The Medical Device Innovation Consortium (MDIC)	https://mdic.org/
	Critical Path Innovation Meetings (CPIM)	https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/critical-path-innovation-meetings-cpim
Collaborative Communities	The FDA currently participates as a member of several collaborative communities, which have been established and are managed and controlled by external stakeholders.	https://www.fda.gov/about-fda/cdrh-strategic-priorities-and-updates/collaborative-communities-addressing-health-care-challenges-together
	Toolkit	https://www.fda.gov/media/116467/download
	Collaborative Community on Ophthalmic Imaging	https://cc-oi.org/?
	National Evaluation System for health Technology Coordinating Center (NESTcc) Collaborative Community	https://nestcc.org/nestcc-one-of-the-first-collaborative-communities-with-fda-participation/
	Standardizing Laboratory Practices in Pharmacogenomics Initiative (STRIPE) Collaborative Community	http://www.stopadr.org/stripe
	International Liquid Biopsy Standardization Alliance (ILSA)	https://fnih.org/our-programs/biomarkers-consortium/programs/ilsa
	Xavier Artificial Intelligence (AI) World Consortium	https://www.xavierhealth.org/ai-summit-registration/
	Case for Quality Collaborative Community	https://mdic.org/program/case-for-quality/
	Heart Valve Collaboratory (HVC)	https://www.heartvalvecollaboratory.org/
	Wound Care Collaborative Community	https://www.woundcarecc.org/
	Pathology Innovation Collaborative Community (PICC)	https://pathologyinnovationcc.org/
	RESCUE (REducing SuiCide Rates Amongst IndividUals with DiabEtes) Collaborative Community	https://www.rescuediabetes.com
	MedTech Color Collaborative Community	https://medtechcolor.org/collaborative-community/
	Digital Health Measurement Collaborative Community (DATAcc)	https://datacc.dimesociety.org/