DataTools4Heart

A European Health Data Toolbox for Enhancing Cardiology Data Interoperability, Reusability and Privacy

Milestone 1:
Clinical acceptance criteria

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Lead Beneficiary	UMCU
Author(s)	Machteld Boonstra Saskia Haitjema
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Acronyms

AI: artificial intelligence

MDR: medical device regulation

IVDR: in-vitro diagnostic regulation

GDPR: General Data Protection Regulation

DGA: Data Governance Act

MSR: Market Surveillance Regulation

DPIA: data protection impact assessment

DPA: data processing agreement

1   Introduction

Continuously, novel digital health care applications are being developed, such as clinical decision support or recommender systems. Especially with this increasing availability of data from the electronic healthcare records (EHR) and the possibility to train complex multi-model AI, there is a considerable potential for AI-models to enhance clinical care. With the large amount of data currently becoming accessible for research, tools are continuously being developed, but implementation of tools remains scarce. This may be due to (technical) feasibility, generalizability, or clinical applicability issues, incomplete compliance to quality standards of tools or sometimes even due to irrelevance of the novel tool to clinical practice, as the tool is not likely to improve clinical care or streamline clinical processes. Thus, whereas the opportunities for AI in healthcare seem promising, prior to implementation, developed models require careful evaluation on their quality (performance, safety), applicability and usability to ensure safe and responsible application and implementation of AI in healthcare.

Therefore, ideally when developing this model, ultimately the end-goal (i.e., clinical implementation) should be taken into account. Therefore, from the very start of the development (i.e., idea generation), regulatory, ethical, clinical and technical aspects should be taken into account. To streamline the development of novel tools and make sure that tools being developed are required and applicable in clinical practice, we summarize important clinical and healthcare requirements for implementation to aid the successful application and added value for clinical care. We therefore focus on various aspects of clinical and health-care requirements, including ethical, privacy, and clinical aspects and map this to the current laws and guidelines for the development and implantation of AI-tools. We propose a first draft of the general acceptance criteria for developed models, and map this to the different phases for model development and implementation.

1.1   Challenges in the implementation of clinical AI tools

Even though health care professionals have a positive attitude regarding the progress in AI and are willing to implement AI-tools within clinical practice, to streamline administrative processes, improve quality of care and standardize interpretation, a lack of trust sometimes remains.[1,2] Additionally, as medical-technical regulation is rather strict and focussed on protecting safety of patients, implementation of these tools is hampered. Generally, clinicians agree on the fact that clinical AI will not replace clinicians, but rather add to the shared decision making during clinical processes and therefore clinical AI plays an additive role. However, the extent to which end-users will accept tools significantly depends on the trust placed within the tools.

Factors identified as having an influence on the adoption of clinical AI are perceived usefulness, user experience, model accuracy, efficiency, cost-effectiveness, interpretability, data security measures and privacy protection capability.[1,2] Important aspects and information identified when aiming to implement and use clinical AI are medical problem and context, training data quality, interpretability and measures to identify and prevent bias. Additionally, training sample size and quality, data pre-processing, training process and measures to reduce overfitting are identified as important aspects. The FUTURE-AI guidelines[3] and Dutch guidelines on valuable AI-development[4] provides clear guidelines to facilitate the development, evaluation, implementation and monitoring of developed

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[1] Chen M, et al. Acceptance of clinical artificial intelligence among physicians and medical students: A systematic review with cross-sectional survey. Front Med (Lausanne). 2022 Aug 31;9:990604. Doi: 10.3389/fmed.2022.990604.

[2] Zahlan A, et al. Artificial intelligence innovation in healthcare: Literature review, exploratory analysis, and future research. Technology in Society. 2023 Jul 5:102321. Doi: 10.1016/j.techsoc.2023.102321

[3] Future-ai.eu

[4] https://www.datavoorgezondheid.nl/documenten/publicaties/2021/12/17/guideline-for-high-quality-diagnostic-and-prognostic-applications-of-ai-in-healthcare

clinical AI tools, thereby focusing on technical aspects of the AI models (e.g., generalizability, traceability, fairness, data quality). Additionally, the Dutch ministry of health developed a funnel on valuable AI development [5], which also focuses on the quality and performance of a CE-marked tool, aimed towards the development of effective, qualitative and safe clinical AI tools. This funnel is initiated to further enhance the development and implementation of valuable clinical AI tools, interdisciplinary collaboration, knowledge and mapping of regulatory standards and clear mapping of the integration of the clinical AI tool within clinical workflow likely provides improved adoption of clinical AI tools, thereby focusing on aspects not regulated in existing legislation[5]. Importantly, throughout the development, validation and implementation of clinical AI tools, protecting patient privacy and data security are core aspects. [6]

1.1.1   Technological push versus technological pull

Currently, technological advancements are often driven by the technological push; there is a new technology (AI-method, increased data availability) which is moulded into a clinical software or tool. However, the developed tool may not necessarily address clinical need. Rather the development should be driven by technological pull, aiming to fill a predefined gap within current clinical practice. Therefore, in the earliest phases of the development of the clinical tool, this should be accounted for, thereby assuring that the development of clinical AI is driven by a clinical need and supported by advancements in technology. From a clinical perspective, acceptance and adoption of AI tools will depend on a combination of usability, added value to current clinical practice and fit within clinical workflow, by defining the clinical gap and intended use of the product, and whether it meets required performance, safety and security standards as stipulated in the regulations.

2   Acceptance criteria

Acceptance criteria are conditions that a product must meet to be accepted by the end-user. Generally, these are unique for each end-user and specific for the clinical AI tool. In the medical context, acceptance criteria allow for the objective evaluation of usability, safety and performance of the clinical AI tool and are typically obtained from clinical data from benchmark studies. Such acceptance criteria are stipulated in different legislations and regulations, such as the medical device and in-vitro diagnostic regulation (MDR/IVDR), Artificial intelligence (AI)-act regulating the safety and performance requirements based on the intended use of clinical AI tools, the General Data Protection Regulation (GDPR) and the Data Governance Act (DGA), to protect patient privacy and data security in the development and application of clinical AI models.

Clinical evaluation of the developed tool provides proof to substantiate the tool meets clinical standards and expectations according to the claim that is made by the legal manufacturer. This means taking into account the intended use and performing a clinical evaluation study according to an assigned risk-classification, as is stipulated in the MDR, thereby assuming the clinical *need* for the novel tool, which is however not defined in these regulations. By defining the intended use, the acceptance criteria are typically defined by setting the objectives for clinical evaluation in a clinical evaluation plan; this evaluation should allow for the demonstration that novel tools meet or outperform the acceptance criteria and add to standard of care, which is currently regulated in the existing legislations or guidelines. Measures of the required performance and safety can for example be provided as weighted average with 95% confidence interval, or medians with interquartile ranges. In this context, benchmarking devices provides evidence whether tools perform within the same range or (preferably)

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[5] https://www.datavoorgezondheid.nl/documenten/publicaties/2021/07/15/innovation-funnel-for-valuable-ai-in-healthcare
[6] Jongsma KR. Acht misvattingen over AI in de zorg [Eight misconceptions about AI in healthcare]. Ned Tijdschr Geneeskd. 2023 Apr 13;167:D7578. Dutch.

outperform on-market devices, if that is the claim the manufacturer decides to make. The regulations however do not stipulate the assessment of the clinical *need* for a clinical AI tool thereby specifically focussing on defined end-users, which may be even more crucial when aiming for adoption of a clinical AI tool.

Next to the acceptance criteria designed to substantiate the claims made regarding the intended use and assuring the claims made when describing the clinical tools are met, acceptance criteria should also focus on defining the clinical added value, comparison to standard of care and specific benefit (either monetary, time, efficiency or other) for end-users when implemented within clinical workflow. For example, the application of the tool provides a clear time benefit and relieves staff in their workload. Additionally, besides assessing whether a tool meets required performance, user-satisfaction, and fits within clinical workflow. In the current document, we will focus on defining clinical acceptance criteria to optimize the adoption of clinical AI models, on top of/in synergy with the fact that the derived clinical AI models should be developed and implemented according to the local, national and EU-regulations and legislations.

2.1 Defining acceptance criteria

Ultimately, in an early stage of the project, acceptance criteria should be defined. In the process of defining acceptance criteria, end-users should be involved. To this end, directly after the idea generation, stakeholders should be identified according to the envisioned end-product (e.g., physicians and patients together during shared decision making). By defining the stakeholders, perspective on envisioned end-product from either clinical, institutional, technicical regulatory, insurance, patient, or research standpoints can be obtained and taken into account in an early stage of the project. Continuous involvement during the design, development, evaluation and validation phases will allow for tool development addressing a clinical need, meeting clinical and regulatory standards. Initiating multidisciplinary teams including all stakeholders will benefit clinical implementation in the end, as in an early stage of the project, important aspects can be taken into account.

When defining acceptance criteria in an early stage of the project, it is important to specify a user story to guarantee that the specific clinical context is taken into account and tools are mapped within the clinical workflow. Additionally, other devices designed to address the intended use, should be identified (e.g., in a market scan to determine the minimal performance standards the tool should meet. When establishing the acceptance criteria, the developer should take into account the criteria are 1) measurable, 2) testable, and 3) achievable and described in an applicable range, not too narrow or broad.

2.2 Clinical adoption of tools

In its core, clinical AI tools will generally be accepted and adopted:

1. if the tool adds value to current clinical practice,
2. if the tool can be implemented and fits within the current clinical workflow,
3. if the tool meets user satisfaction,
4. if the tool outperforms current state-of-the-art solutions,
5. if evaluated and validated in the intended use within the clinical context,
6. tools are not harmful and safe to use, as stipulated in the MDR,
7. set up the risk-management to protect patient privacy and data security,
8. the development process is controlled and documented,
9. technical and model performance is stable, and

10. set up post market surveillance and identifying potential biases and implementing mitigation strategies.

When reviewing the regulations, items 1-3 are not taken into account, except when specifically included in the intended use or claims made by the developer. However, these items are very important to ensure the adoption by the end-user, either clinicians, patients or technicians; if tools do not meet their expectations or add to their clinical workflow, likeliness of adoption will severely decrease. The adoption of the clinical AI tool however will also rely upon the discretion of the healthcare professional, even when recommended in guidelines, e.g., treating physicians may deviate from the use of the clinically (accepted) AI tool in specific cases or due to specific circumstances.

2.2.1 General example of acceptance criteria

An example of a broad scenario to define acceptance criteria for a 'general AI tool': As a [stakeholder], I want to [implement/use/get] a clinical AI tool to [intended use] in [setting/clinical context/timing]. Even though the intended use and setting/clinical context for application of the clinical tool will be the same, per stakeholder, acceptance criteria will differ. Some general examples as identified per stakeholder can be different for the different stakeholders, as presented in Table 1.

To ensure clinical adoption, the clinical AI developer should to assess these different aspects in an early stage of the project, as this can affect especially the end product. Generally, model developers require to establish (a) robust dataset(s) allowing for several testing strategies, both on bias level as well as variation in input variables and through the multidisciplinary group, the end-product can be optimized, in terms of technical, legal/regulatory and usability aspects.

Table 1 Stakeholders and definition of general acceptance criteria

Stakeholder	General aspects of attention for acceptance criteria
Clinicians	**Regulated**: Medical context and cohort (intended-use) Technical documentation and training material Clinical evaluation (level of confidence) Model performance and monitoring (clinical validation and post-market surveillance) Unexpected findings **Not regulated**: Implementation strategy and embedding within clinical workflow Usability Should not add to current workload
Patients	**Regulated**: Model performance Bias in subgroups and mitigation strategies Privacy and autonomy preservation **Not regulated**: Usability for shared decision making / individual use Tailored to educational / socio-economic level
Institutions/legal	**Regulated**: Risk-management Authorization of operators (e.g., nurses, clinicians, technicians, specialists) Privacy of patients

	In accordance to local, national and EU regulations **Not regulated**: Cost-benefit Liability and accountability Responsibility during failure and acceptability limits
Technicians (implementation / maintenance / monitoring)	**Regulated**: Requires no outgoing or safe connection to external servers **Not regulated**: Fit within the ICT-workflow Code is transparent and accessible Monitoring tools can be implemented and linked to the model Usability dashboarding for monitoring

2.3   Defining acceptance criteria

In the process of defining acceptance criteria, three questions are of importance:

1. Can we develop the clinical AI tool from a technological perspective?
2. Are we allowed to develop clinical AI tool with the defined intended use?
3. Do we want to develop the clinical AI tool with the defined intended use case?

When working from a technology push perspective, question 1 is answered first; e.g., availability of data, novelty of AI-techniques, whereafter the fit within the current regulations is defined. Reflected in the fact that most clinical AI tools are not included in current clinical care or mentioned in guidelines, developers may not always ask the third question. Incomplete acceptance can be partially attributed due to technical development of the clinical AI tools, e.g., are they generalizable, published open-access, robust to variations in input data, externally validated but another part can be attributed to the lack of clinical need and usability for the clinical AI tool. Whereas guidelines are currently emerging on the development and technical aspects on valuable clinical AI models (FUTURE-AI), there is no specific focus on clinical usability and need. When reversing the order of the asked questions 1-3 will allow for a 'technological pull' strategy; starting off with the clinical need, addressing regulatory aspects and finding the technical best fit for the *needed* clinical AI tool. This allows for a shift in focus when developing the tool; instead of working from question can we develop this clinical AI tool, we shift to working from the question do we *clinically need* to develop this AI tool.

To provide guides towards the implementation of clinically valuable AI tools, we present the initial two steps focussing on idea generation and setting up model development, thereby taking into account requirements focussed on clinical validation, evaluation, implementation and monitoring. Various aspects should be taken into account when aiming for clinical adoption and implementation. After the first two steps, models will typically be validated and evaluated (step 3) and implemented and monitored (step 4). Documentation on the study procedures, technology used, risk-management, data privacy impact assessment, cost-benefit, liability and others will iteratively be updated according to findings in both steps. Taking into account the requirements for the moments of clinical implementation, allows for early anticipation on requirements later in the process.

Table 2 Initial steps towards implementing valuable clinical AI tools

Step 1	Idea generation: Identification of the current clinical gap and the derivation of appropriate research questions is the main purpose.	
	Setting/contextual:	- Clear definition of medical problem framed within the clinical context, definition of the intended-use of the clinical AI tool (e.g., supporting what clinical decision during shared decision making?) - Describing the embedding of the proposed solution in the clinical workflow - Identification of barriers for clinical adoption. - Identification of the end-users and stakeholders of the clinical AI tool and cost-benefit assessment per stakeholder group. - Clear definition on the societal/clinical added value, impact and risk-benefits overall and within different settings. - Identification of similar products and establishment of minimal acceptance criteria. - Study protocol is derived for model development and evaluation; containing a thorough evaluation of literature, current solutions, initial evaluation and validation strategy and the defined set of acceptance criteria.
	Model development	- Definition of a minimal dataset - Assessment of data availability and sufficiency for clinical AI tool development. - Initial setup of the clinical evaluation plan - Initial setup of the technical documentation.
	Model evaluation and implementation	- Embedding within clinical workflow. - Initial assessment of clinical AI tool implementation within ICT-infrastructure - Assessment of end-user interaction with tool.
	Regulation	- Framing initial privacy, security, ethics, (medical) legal regulation context. - Initial risk-assessment on information security and risk of model failure and expected effect. In accordance, the initial risk-management plan should be derived. - Initial data protection impact assessment (DPIA) and the implementation of privacy by design for the research / model development phase. - Identification of sociocultural barriers of clinical AI adoption. - Liability analysis and assessment requirements for medical device and risk-classification.
Step 2	Model evaluation and validation according to the intended clinical AI tool	
	Setting/contextual:	- Clear description of the problem application and research question. - Comparison to already existing clinical AI solutions to define the added value of the model and reaching the acceptance criteria defined within the project. - Initial cost-benefit analysis.
	Model development	- Privacy by design; minimize the use of personal data in the development of the model and test for different input variables.

		- Study protocol is updated for model evaluation, including a description of the current setting, model evaluation and validation plans. - Finalizing the model, thereby mapping safety issues and minimizing risks of privacy breach. - Automated logging and version control during model development.
Model evaluation and implementation		- Initial model performance assessment and comparison of different model designs. - Finalizing the clinical evaluation plan and defining monitoring and mitigation of harmful and undesired effects, finalize stop criteria to stop clinical validation based to protect patient safety. - Initial setup of the technical documentation. - Interpretability and transparency on model development and design. - Error margins and deviation in model performance for different subpopulations is described. - Defined ICT-framework for model embedding. - Design and re-iteration of end-user interface - Interoperability according to universal standards for data modelling. - Defining instructions for use, describing boundary conditions. Adapting the clinical AI tool to implement required bounds or provide warnings - User autonomy is ensured and described for the application of the clinical AI tool.
Regulation		- Identification of the CE-class based on the intended use. - Update DPIA with the evaluation and implementation plan - Update of risk-management plan and risk-benefit analysis: - Describe eliminated risks - Describe unforeseen risks encountered during the development phase - Describe containment and control measures - identification of residual risks - Risk-classification on information security. - If required, data processing agreements are established with external partners - Official approval by the ethical board for the study protocol is obtained. This also includes finalizing the DPIA for the evaluation studies.

2.4   General requirements on technical model documentation

When developing a model, according to the MDR and to obtain CE-mark, adequate documentation on the development process is required. Therefore, maintaining the technical documentation throughout the development process from idea generation to implementation and post-market surveillance, is warranted. Specific topics addressed in this documentation can be:

- Input variables, definition of variables and data coding standards (data dictionary).
- Cohort sample size
- Cohort inclusion criteria / study cohort

- Cohort and data characteristics
- Pre-processing steps
- Performed data quality checks
- Measures to identify and prevent bias
- Measures to reduce overfitting
- Missing data handling
- Training data source
- Model parameters description
- Data collection and preparation
  - Sample size
  - Obtaining dataset
  - Defining ground truth
  - Data annotation
  - Data quality assessment
  - Data coding standards
  - Pre-processing
- End-user training
- Privacy and security measures
- Model selection and interpretability
- Internal verification, explainability, assessment of overfitting (measures)
- Transparency of the modeling process (regulation, setting up the PDMS)
- Internal validation
- Usability; ease of use, (aimed) embedding within clinical workflow
- Description on the intended use; e.g., what should the model provide, in which clinical context/setting and who are the end-users.

3 Relevant regulatory aspects

As an overview, we briefly provide an overview of the different regulations and legislation related to the development and implementation of clinical AI tools.

3.1 Safety and intended use

Medical device regulation (**MDR**): entered into effect on 26-05-2021. Manufacturers of medical devices must comply with the regulation when placing new medical devices on the EU market. Most clinical AI tools are considered medical devices and need to be assessed by notified bodies. The MDR aims to guarantee safety and effectiveness of medical devices. MDR applies to devices that come into direct contact with humans. The MDR is focussed on the defined intended use, clinical impact and evaluation, most focused on ensuring safety and performance of use. Assessment by a notified body may lead to a CE-mark. **CE** mark: a mark with which the manufacturer or importer affirms the conformity with the European health, safety and environmental protection standards, it is not a quality indicator or a certification mark. Different devices are grouped in different classes, depending on the risk. MDR refers to state-of-the-art software development, meaning compliance with relevant ISO norms such as 13485 (quality management systems), 14971 (risk management) and 62304 (software development life cycle).

Artificial intelligence (**AI**)-act: currently proposed by the EU. The regulation aims to introduce a common regulatory and legal framework for AI. The main purpose is to aid the development of safe,

transparent, traceable and non-discriminating AI-algorithms. AI-tools will be monitored depending on the level of risk from the (proposed) AI solution.

3.2 Patient privacy and data security

General Data Protection Regulation (**GDPR**): entered into effect on 25-05-2018. Regulation on information privacy in the European Union and the European Economic Area intended to protect (patient) privacy. The regulation serves as a comprehensive data protection regulation.

Data Governance Act (**DGA**): entered into effect on 23-06-2022. Regulation to create a secure environment for the processing and re-use of public sector data for purposes other than the ones for which the data was originally collected (e.g., re-use of health data for research purposes). It focusses on data sharing, access and interoperability within the EU.

3.3 Monitoring of safety after clinical implementation

Market Surveillance Regulation (**MSR**): to ensure consistency of the application of rules of the developed clinical AI tool. It provides regulation on the monitoring of clinical AI tools after clinical evaluation and implementation. Post-market surveillance is also part of the MDR.

3.4 Overview of local documentation for model development

On top of the regulatory framework provided by the EU for the development of clinical AI tools, local authorities may require additional information. In Table 3, an overview of documentation required for 1) ethical approval, 2) internal data extraction and processing and 3) data processing by external partners is provided specifically for research designed to re-use electronic health record data.

Table 3 Overview required local documentation for the re-use

Partner	Required documentation
KUH	**Ethical approval** - Study protocol - Informed consent form - Variable list **Data extraction and processing (internal, of note: varies by region/hospital in Sweden)** - Local data extraction form with ethics approval - local approval at each hospital from head of hospital **Data processing (external partners)** - Approval by hospital - DPA at least, depends on external party within the EU or other.
UCLH	**Ethical approval** - Organisation information document - non-commercially sponsored studies. Including: agreement between local center and NHS / HSC organization, Finance provisions, Material transfer provisions (if applicable), Data Processing Agreement, Data Sharing Agreement, Intellectual Properties Rights, - Study protocol, details of all investigators, description of patient and/or staff engagement, Data specification, Data Storage, Analytical plan and Project Governance - Data flow overview - confirmation of organisational sponsorship and insurance, and other study materials such as patient consent forms, patient information forms etc. if applicable to the study.

	Data extraction and processing (internal) - Cover letter - Study Protocol - Data flow overview - Integrated Research Application System form, including information on study protocol, details of all investigators, description of patient and/or staff engagement, patient population, data specification, data storage and flow, analytical plan and project Governance **Data processing (external partners)** - DPA
VHIR	**Ethical approval** [not yet provided] **Data extraction and processing (internal)** [not yet provided] **Data processing (external partners)** [not yet provided]
GEM	**Ethical approval** - Umbrella study protocol. - General Information on Data Processing, including DPIA - Form for specific center non-profit or co-financed non-profit observational study (with drug, device or other) **Data extraction and processing (internal)** - List of required variables **Data processing (external partners)** - Data processing agreement, processing master DT4H DPA for approval by local legal office
ICRC	**Ethical approval** - Cover letter to the ethical board. - Study protocol (both umbrella protocol and protocol synopsis) **Data extraction and processing (internal)** - Data Processing Impact Assessment **Data processing (external partners)** - Data Processing Agreement
BUCH	**Ethical approval** [not yet provided] **Data extraction and processing (internal)** [not yet provided] **Data processing (external partners)** [not yet provided]
UMCU	**Ethical approval** - Cover letter providing a short description and most important aspects of the study (A1-form) - Study protocol (CCMO C1-form) with a description of the proposed study procedures and data processing. - Data Protection Impact Assessment (DPIA) and data management plan (DMP). - When applicable: Information and consent form (ICF) for patients. When applying for a waiver for informed consent, ICF does not have to be submitted, instead a rationale for the waiver of informed consent should be provided. **Data extraction and processing (internal)** - Application form for the re-use request of clinical data (research data management application form). **Data processing (external partners)** - Data processing agreement, local format. - Access to data and local environment of choice by the principal investigator

AUMC	**Ethical approval** - Cover letter providing a short description and most important aspects of the study (A1-form) - Study protocol (CCMO C1-form) with a description of the proposed study procedures and data processing. - Data Protection Impact Assessment (DPIA) and data management plan (DMP). - When applicable: Information and consent form (ICF) for patients. When applying for a waiver for informed consent, ICF does not have to be submitted, instead a rationale for the waiver of informed consent should be provided. **Data extraction and processing (internal)** - Data management plan (living document) - Application form for the re-use request of clinical data (research data management application form). **Data processing (external partners)** - Data processing agreement, local format. - Access to data and local environment of choice by the principal investigator