INNO4COV-19

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Abbreviation and Acronyms

AI – Artificial Intelligence

ELISA – Enzyme-linked immuno sorbent assay

ISO – International Organization for Standardization

IVD – In vitro diagnostic medical device

MD – Medical device

QMS – Quality management system

RT-PCR – Reverse transcriptase polymerase chain reaction

TPP – Target product profiles

VITO – Flemish Institute for Technological Research

WHO – World Health Organization

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Contents

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Executive Summary

This document provides information about the relevant framework and specifications for medical diagnostic devices and screening systems that are required in order to reach the market. The main objectives of this report are to provide i) more detailed information on the framework for development of devices in the context of COVID-19 diagnosis and screening, ii) a Specifications Sheet template with instructions for use by test case providers/future users of the service platform, and iii) a guideline for implementation of the Specifications Sheet in the INNO4COV-19 service platform workflow.

This report describes the technical restrictions and critical process parameters for two major categories of diagnostic and screening systems, being *in vitro* diagnostic and screening assays/devices and artificial intelligence (AI) based diagnostic tools.

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1. Framework for development of diagnostic and screening systems

In preparing the Specification Sheet templates two categories of emerging and existing technologies for diagnosis and screening have been considered which are focused on priority use case scenarios to address the greatest needs.

The first category involves *in vitro* diagnostic and screening tests and devices based on molecular detection (e.g. RT-PCR), antigen detection (e.g. ELISA, lateral flow assay) and antibody detection (e.g. ELISA). These are among the most common types of tests already on the market to tackle the SARS-Cov-2 pandemic, while new tests with different intended use and/or improved performance are under development in large numbers (FIND COVID-19 Diagnostics Pipeline, https://www.finddx.org/covid-19/pipeline/).

The second category is related to AI diagnostic tools based on machine learning algorithms using digitalized diagnostic or screening data. These are gaining interest at a fast pace to control the COVID-19 spread, as they allow for fast, automated data analysis (detection, classification, segmentation, etc) and sharing to enable easy screening, decision making, and follow-up of patients (https://www.coe.int/en/web/artificial-intelligence/ai-covid19).

1.1 Regulatory framework

In Europe medical devices need to be developed and placed on the market in compliance with the new Medical Device Regulation MDR 2017/745 (replacing the current Directive 93/42/EEC) and In Vitro Diagnostic (IVD) devices in compliance with the IVDR 2017/746 (replacing IVD Directive 98/79/EC). When assessing conformity with the legislation and prior to issuing a certification (CE mark), the manufacturer must evaluate the performance and safety of the device, and capture the data in the instructions for use and Technical Documentation of the device. In the justified urgency circumstances of the COVID-19 outbreak, MD and IVD addressing a COVID-19 unmet need can be authorized for commercialization within a Member State territory by the Member State without having completed the conformity assessment procedure yet.

The collection of the safety and performance data in conformity with the European Harmonized Standards is considered state of the art. Many of these standards are ISO standards which are harmonized in Europe.

In addition to conducting analytical and clinical performance studies, the performance of devices may be validated, e.g. in reference laboratories, academic institutions or national regulatory agencies. Such validation is not legally obligatory, but is highly recommended for public health decision making, especially in the context of the current COVID-19 crisis.

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In vitro diagnostic and screening tests and devices, described above, are intended for the purpose of surveillance (detect acute or past exposure or infection), case management of suspects, contact tracing (detect (a)symptomatic acute infection), monitoring response or recovery, prognosis, vaccine response, and/or environmental monitoring. Based on their intended use, they fit the definition of an IVD device, and can be divided into classes D and C of the IVDR 2017/746.

MDCG 2019-11 on the classification of software provides guidance on the classification of computer aided detection systems as Decision Support Software, which combines general medical information databases and algorithms with patient-specific data. They are intended to provide healthcare professionals and/or users with recommendations for diagnosis, prognosis, monitoring and/or treatment of individual patients, and are qualified as Medical Device Software (MDSW).

1.2. Medical device development life cycle

During its development life cycle, a medical device product goes through distinct phases, as depicted in Figure 1. These consist of i) conception and prototyping, ii) classification and development of a regulatory plan, iii) installation of a quality management system (QMS), iv) product development, including design control and risk management, and v) product launch, including technology transfer to enable production, product registration and marketing.

Figure 1: Medical device development life cycle

Harmonized international standard EN ISO 13485:2016 is designed to be used by organizations involved in the design, production, installation and servicing of medical devices and related services. It contains a process-oriented approach and helps organizations to implement a quality management system.

For medical device software, international standard IEC 62304 defines software development life cycle requirements.

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For both medical devices and medical device software a product development methodology and approach, described in the aforementioned harmonized standards can be used as a guidance. An example of such approach is the V-model, shown in Figure 2, in which specifications related to user requirements, product functions and product design are represented. These have been taken into account in the Specification Sheet templates, described in section 2.

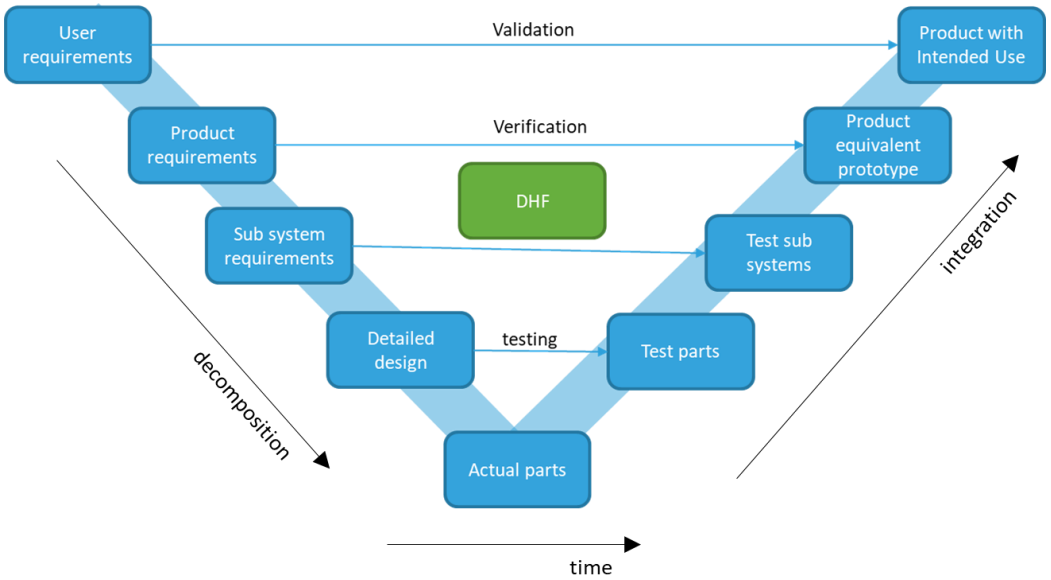

Figure 2: V-model of medical device development. Traceability of all design controls throughout the product development process, as required by the applicable regulations, are kept in the Design History File (DHF).

2. Specifications Sheet template

The Specifications Sheet template for the first category of in vitro diagnostic and screening tests and devices has been based on the Target Product Profiles (TPP) for priority COVID-19 diagnostics, published by the WHO in September 2020 (WHO, 2020). They describe the desirable and minimally acceptable profiles for four different intended uses for SARS-CoV-2 testing:

- Point of care test for suspected COVID-19 cases and their close contacts to diagnose acute SARS-CoV-2 infection in areas where reference assay testing is unavailable, or turnaround times obviate clinical utility (e.g. lateral flow antigen tests, isothermal PCR)
- Test for diagnosis or confirmation of acute or subacute SARS-CoV-2 infection, suitable for low or high-volume needs (e.g. RT-PCR)
- Point of care test for prior infection with SARS-CoV-2 (e.g. antibody flow strip assay)
- Test for prior infection with SARS-CoV-2 for moderate to high volume needs (e.g. ELISA)

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For compilation of the Specifications Sheet template for AI based diagnostic and screening systems, specific guidelines in the context of SARS-CoV-19 testing are not yet available. Here, we based ourselves on available literature on AI tools for analysis of medical imaging data (e.g. from X-ray or computerized tomography scans) (Morozov SP et al., 2019).

2.1. *In vitro* diagnostic and screening assays and devices

The Specifications Sheet template for in vitro diagnostic and screening assays and devices is added as a separate excel file to this report (Annex I). The key performance features are explained in Table 1. A completed template for the pilot Test Case of partner iMM is available in Annex II.

Table 1. Specifications Sheet template for *in vitro* diagnostic and screening assays – description of key performance features

Key performance feature	Description
APPLICATION ASPECTS	
Intended use	The use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements or as specified by the manufacturer in the performance evaluation. Intended uses for SARS-CoV-2 testing and technologies include surveillance (detect acute or past exposure or infection), case management of suspects, contact tracing (detect (a)symptomatic acute infection), monitoring response or recovery, prognosis, vaccine response, environmental monitoring, etc.
Target use setting	Setting according to volume needs (low-moderate-high): reference laboratories, central hospital laboratories, mobile laboratories, triage centers (emergency units, mobile units, contact tracers), point of care, home, etc.
Target population/patient	Patient with particular suspicious symptoms who has had known contact with probable or confirmed COVID-19 patient or living in cluster area or community transmission; close contacts (with or without symptoms) of confirmed COVID-19 patients; suspected COVID-19 cases requiring confirmation or exclusion of COVID-19 infection, etc.
Sample type	Nasopharangeal/orophharyngeal swab or wash, nasal wash, bronchalveolar wash, sputum, saliva, blood, serum, plasma, etc. Samples that are easiest to collect, are preferred.
Sample collection	Method and compatible devices for sample collection, e.g. swab materials.
Target molecule	Analyte(s) to be detected: SARS-CoV-2 biomarker (RNA, proteins/antigens, antibody isotypes) specific for active or prior infection.
Detection principle	Scientific principle of the test method, including biomolecular recognition of a target marker associated with a COVID-19 infection, and development of read-out signal.

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Test kit format	Components of the test kit required for sample collection, processing and analysis, including reagents, controls, consumables, etc.
End user profile	Trained health care worker or lab technician in healthcare facilities, trained lay worker in community level facilities, patient self-administered, etc.
Training needs end user, duration	Training on sample collection, test procedure, data interpretation, QC and biosafety, required for test performance, including instructions for use and quick reference guide(s), training format (online modules, hands-on).
QUALITY CONTROL	
Positive control	Identity and nature of positive control material for the full process, provided in the kit.
Negative control	Identity and nature of negative control material for the full process, provided in the kit.
Internal control	Internal control material and/or method for sample flow or migration as an area or region within the test or testing device, e.g. RNA extraction control.
Calibration control	Calibration control material and/or method for the reader, if applicable.
Type of data analysis	Qualitative (positive/negative), semi-quantitative or quantitative.
Result output type	Type of data and expected results, e.g. binary diagnosis, categorical assessment, scoring, image vizualization, etc.
Data interpretation type	Visual manual read and/or digital hardware read (proprietary or smartphone application with connectivity); mathematical prediction model and/or thresholds/cut-offs for each analyte, including borderline or equivocal results; patient identification capacity.
Test acceptance criteria	Performance and qualification criteria of positive and negative controls, validation status against well characterized samples from patients with past history of PCR-confirmed SARS-CoV-2 infection.
ANALYTICAL PERFORMANCE	
Sensitivity/Limit of detection	The ability of a device to identify the presence of a target marker associated with a COVID-19 infection, e.g. viral loads in patient specimens associated with infectivity, expressed as genomic copies/mL or cycle threshold (Ct) values. Well characterized reference material and international standards should be used, when available, to determine LOD. Currently there is no international standard/units to express LOD; in the interim it can be expressed as the minimal detectable concentration of analyte in well characterized samples from patients with past history of PCR-confirmed SARS-CoV-2 infection.
Specificity	The ability of a device to recognise the absence of a target marker associated with a COVID-19 infection.
PCR efficiency	The ratio of the number of target gene molecules at the end of a PCR cycle divided by the number of target molecules at the start of the same PCR cycle.
Robustness	Capacity of the assay to remain unaffected by minor variations in test situations that may occur over the course of testing in a single laboratory.
Precision	Closeness of agreement between independent test results obtained under stipulated conditions.

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Analysis of cross reactivity	Analysis of reactivity with other human coronaviruses or any other common human diseases, especially those presenting with similar signs and symptoms of COVID-19 (e.g. Influenza A and B, RSV, malaria, dengue).
Analysis of interference	Analysis of common interfering substances.
Reproducibility	Precision under conditions where test results are obtained with the same method on identical test items in different laboratories with different operators using different equipment.
CLINICAL PERFORMANCE	
Clinical sample origin	Hospital laboratories, biobank, mobile laboratories, triage centers (emergency units, mobile units, contact tracers), home, etc.
Study design	Prospective/retrospective sampling, cohort size, inclusion and exclusion criteria, etc.
Ethical approval	Obtained or not, scope.
Sensitivity/Limit of detection	Determination of sensitivity should be against an approved/authorized molecular-based COVID-19 assay.
Specificity	Determination of specificity should be against an approved/authorized molecular-based COVID-19 assay.
PCR efficiency	The ratio of the number of target gene molecules at the end of a PCR cycle divided by the number of target molecules at the start of the same PCR cycle.
Robustness	Capacity of the assay to remain unaffected by minor variations in test situations that may occur over the course of testing in a single laboratory.
Precision	Closeness of agreement between independent test results obtained under stipulated conditions.
Analysis of cross reactivity	Product assessment of clinical specificity should include patients/samples with other human coronaviruses and pathogens in differential diagnosis for presenting signs/symptoms.
Analysis of interference	Analysis of common interfering substances.
Reproducibility	Precision under conditions where test results are obtained with the same method on identical test items in different laboratories with different operators using different equipment.
TEST PROCEDURE	
Sample collection reagents	Use of preservative, anticoagulant.
Sample storage and stability time pre-testing	Maximal time of stability for a dry or preserved sample (in generic preservative), minimal-maximal storage temperature range, packaging.
Sample minimal volume	Minimal sample volume (e.g. single swab and minimal extraction buffer/diluent) required to reach clinically relevant sensitivities and ideally would allow for repeat testing.
Need to transfer a precise volume of sample	Pipetting, or autofill or graduated volume markings on sample transfer device, addition of drops (not considered 'precise' volume requirement).
Sample preparation steps	Need to process the sample before performing the test, e.g. benchtop preparation, sample transfer, sample inactivation step; number of steps.

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Test kit stability and storage conditions	Time stability data to support shelf life requirements, including temperature range, humidity, altitude; indicator of instability or expiration.
Reagents reconstitution	Need to prepare the reagents before utilization.
Stability of kit once opened	Time for single use test after opening the pouch.
Specimen capacity and throughput	Number of individual tests that can be run in parallel, per operator, and time needed.
Safety precautions	Recommended biosafety and chemical safety requirements from sample collection to test result; precautions to minimize the need for such requirements, e.g. materials free of components with a GHS classification H, easy decontamination of instrument surfaces, self-sampling collection device with virus inactivation, etc.
Operating conditions	Conditions related to temperature, relative humidity, light intensity, air cleanliness, altitude.
Number of timed steps	Use of different reagents and/or incubation steps, with the potential for digitally guided workflows and built-in timers.
Time to result	Time from start of sample collection to test result.
Result validity stability	Fixed reading time, storage of test result.
Invalid rate	Percentage of invalid results with correct use by the operator.
Remote connectivity capacity for data capture	Compatibility with readers and other data capture devices, internal memory to store data, capability of remote export of data (USB, LAN, WIFI, Bluetooth), ability to report to country health information management systems using onboard identifier or other personal data protection safeguards.
Additional equipment	Diagnostic platform instrument, non-automated open systems or proprietary automated systems; readers handheld or desktop, battery or solar power operated, potential for digital connectivity.
Need for maintenance/spare parts	Preventive or curative maintenance with duration and performer, frequency of maintenance, need for calibration, need for replacing spare parts and frequency.
Waste/disposal requirements	Routine biohazard waste or incineration of consumables, need for decontamination.
Accessibility	Production scale, pricing, geographical area.
REGULATORY COMPLIANCE	
Target IVD classification	Classification according to IVDR 2017/746.
Quality management system, risk management system	Status of ISO 13485:2016 and ISO 14971:2019 compliance.
Status of regulatory approval	CE mark (or FDA approval), WHO or stringent regulatory authority (SRA) emergency use listing/authorization, WHO prequalification, or other SRA approval.

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2.2. AI diagnostics

The Specifications Sheet template for AI diagnostics is added as a separate excel file to this report (Annex III). The key performance features are explained in Table 2.

Table 2. Specifications sheet for AI diagnostics – description of key performance features

Key performance feature	Description
APPLICATION ASPECTS	
Intended use	The use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements or as specified by the manufacturer in the performance evaluation. Intended uses for SARS-CoV-2 testing and technologies include surveillance (detect acute or past exposure or infection), case management of suspects, contact tracing (detect (a)symptomatic acute infection), monitoring response or recovery, prognosis, vaccine response, environmental monitoring, etc.
Target use setting	Setting according to volume needs (low-moderate-high): reference laboratories, central hospital laboratories, mobile laboratories, triage centers (emergency units, mobile units, contact tracers), home, etc.
Target population/patient	Patient with particular suspicious symptoms who has had known contact with probable or confirmed COVID-19 patient or living in cluster area or community transmission; close contacts (with or without symptoms) of confirmed COVID-19 patients; suspected COVID-19 cases requiring confirmation or exclusion of COVID-19 infection; etc.
Input data type	The type of data required by the model. For example: Image data from X-ray, CT, NMR imaging. DNA sequencing results. Biosensor readout. Information from mobile phone sensors.
Data collection hardware, compatible devices	Hardware required for collection of data. Is the model compatible with data captured by different devices?
Decision taken based on model results	What action is to be taken based on model output? Examples: A subset of processed data will be prioritized for further analysis by a healthcare professional. Model provides population screening, output is basis for referral for further diagnostic testing. Model output provides the basis for determining the course of treatment.
End user profile	Trained health care worker or lab technician in healthcare facilities, trained lay worker in community level facilities, patient self-administered, etc.
Training needs for end user	Training required for use of the product and, if relevant, for the collection of input data. Describe the availability of training courses, instructions for use etc.
MODEL INFORMATION	

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Problem type	The type of problem being minimized by the model, e.g. regression, segmentation, classification. Further details, e.g. number of classes.
Learning model type	The class of machine learning being implemented (supervised, unsupervised, semi-supervised, weak supervision, reinforcement learning)
Algorithm used	The algorithm being applied (e.g. logistic regression, support vector machine, decision tree, convolutional neural network, deep learning)
Type of result output	The type of data output by the model: binary diagnosis, categorical assessment, scoring, image visualization, etc.
DATASET INFORMATION	
Origin of training dataset	The source(s) of the training dataset.
Size of training set	The size of the dataset used. The relative sizes of the training/validation/test sets.
Dataset demographics	Details about the demographic distribution of test subjects in the dataset - gender, ethnicity, age etc. Do these demographics reflect the demographics of the target patient population?
Inclusion criteria	Criteria for inclusion of test subjects or pieces of data into the training set.
Exclusion criteria	Criteria for exclusion of subjects or pieces of data into the training set.
Distribution of test subjects among diagnostic groups	Details of the distribution of test subjects across the relevant classes (e.g. COVID-19 positive / negative based on PCR assay); normal-to-abnormal ratio. Is this distribution appropriate for the intended patient population?
Nature of labeling information	If relevant for the learning model being applied: the type of labelling/tagging information associated with the dataset. Was the data associated with the clinical outcomes / confirmed diagnoses?
Labeling methodology	Methodology used to generate the labels. Eligibility criteria and training required for the labeler. Approach in case of lack of consensus between labels.
ANALYTICAL PERFORMANCE	
Details of test dataset	Was the test dataset from the same source as the training/validation data? If this was independent, provide details of the test set.
Performance metric during model optimization and value achieved	The key performance metric used during the model development and the value achieved for the validation dataset, and for the test dataset. E.g. for binary classification the area under the receiver operator characteristic curve. Similarity coefficient, etc.
Other relevant performance metrics	Any other relevant performance metrics and the values obtained. E.g. for binary classification the confusion matrix and/or the key values derived from the confusion matrix.

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CLINICAL PERFORMANCE	
Status of clinical study	Whether an additional clinical validation study has been carried out or is planned.
Origin of clinical test dataset	What source of data will be used for the clinical study.
Study design	Details of the clinical study design, e.g. prospective/retrospective sampling, sample size, eligibility criteria, randomization and blinding, etc.
Status of ethical approval	Has ethical approval been obtained for the study according to local regulations. What is the scope of the ethical approval?
Labeling methodology	Details of the labeling methodology for the clinical study, if different from those used during the model development. Had a reference/"golden standard" technique been used for verification?
Value of key performance metric and other relevant performance metrics.	If study has been completed, the performance of the product in the study.
TEST PROCEDURE	
Time-to-result	Time from start of sample collection to test result. How does the time taken to compare to existing solutions?
Currently deployed in clinical care settings?	Is the solution currently being used or tested in real-world settings?
Analysis hardware	What are the hardware requirements to run the model? Is the product using cloud infrastructure, running on a local machine, portable device.
Details of additional equipment	Is any additional hardware needed to gather the sample, collect and/or process the data required for the analysis? Is this hardware already typically available in the intended use setting?
Accessibility	Hardware production scale, pricing, running costs. Geographical area being targeted for deployment of the product.
REGULATORY COMPLIANCE	
Target medical device / in vitro diagnostic classification	The intended class of the device according to the EU Medical Device Regulation / In-vitro Diagnostic Regulations.
Quality management system, risk management systems employed	Status of ISO 13485:2016 compliance, ISO 14971:2019 compliance.
Status of regulatory approvals	CE mark (or FDA approval), WHO or stringent regulatory authority (SRA) emergency use listing/authorization, WHO prequalification, or other SRA approval.
Data protection regulation compliance	Compliance with the EU General Data Protection Regulation or other relevant data privacy protection regulations.

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3. Guidelines for implementation in INNO4COV-19 service platform

The Specifications Sheet templates for the two product categories, in vitro diagnostic and screening tests/devices and AI diagnostics, have been devised to identify the technical restrictions and critical process parameters for their intended use, and collect information on the current development status of new technologies applying for services from the INNO4COV-19 platform.

Product specific aspects related to application, assay quality control, AI model, AI training dataset information, analytical and clinical performance, regulatory compliance and test procedure are included in the Sheets (described in section 2). They are intended to allow smooth translation into a technology development proposal to be performed for the test case/client, through identifying the needs for product testing, verification, validation and certifications.

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4. Summary

In this report, specifications related to user requirements, product functions and design, and performance have been provided for two categories of diagnostic and screening systems: *in vitro* diagnostic and screening assays/devices and AI based diagnostic tools. These represent major categories for priority use in the current SARS-CoV-2 pandemic crisis.

The report consisted of:

- information on the framework for development of devices in the context of COVID-19 diagnosis and screening;
- Specifications Sheet templates with instructions for use for the two product categories;
- a guideline for implementation of the Specifications Sheets in the INNO4COV-19 service platform workflow.

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References

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Morozov SP, Vladzymyrskyy AV, Klyashtornyy VG, Andreychencko AE, Kulberg NS, Gombolevsky VA, Sergunova KA, 2019. Clinical acceptance of software based on artificial intelligence technologies (radiology). Series 'Best practices in medical imaging', Issue 57, 45 p.

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Annexes

D2.1_Annex I_Specification Sheet template_IVD assays_v3.xlsx

D2.1_Annex II_Specification Sheet iMM.xlsx

D2.1_Annex III_Specification Sheet template_AI_v3.xlsx

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