Clinical Trials Office

Guide to the submission of a request for authorisation of a Clinical Trial involving the use of Artificial Intelligence (AI) or Machine Learning (ML) systems

AIFA Italian Medicines Agency

AIFA working group drafting the guide
Coordination: D. Gramaglia
Clinical Trials Office: D. Gramaglia, D. A. Dri, M. Massella, N.M. Verrelli, G. Praticò
Pre-Authorization Department: S. Petraglia
Innovation and Pharmaceutical Strategy Division: P. Foggi, M. Di Marzo
Innovation & EMA Scientific Advice Office: E. Agricola
Flow charts and tables: D. A. Dri
Text: D. A. Dri, E. Agricola, M. Di Marzo, M. Massella, N.M. Verrelli

CONTENTS

Agenzia Italiana del Farmaco   ⊙ Via del Tritone, 181 - 00187 Roma   ☏ (+39) 06.59.78.401   🌐 www.aifa.gov.it

1. INTRODUCTION

Over the last few years, there has been an increase in the number of clinical applications based on the use of Artificial Intelligence (AI) or Machine Learning (ML) systems, which has had an impact also on the activities of the Competent Authorities (CAs) involved in the evaluation of Clinical Trials (CTs).
The application of AI or ML systems can support a faster access to innovative medicinal products and personalised medicine, resulting in a rapid evolution of the CTs setting, that is now enriched by incorporating the developments of scientific and technological innovation. In any case, robust CTs remain the main sources of scientific evidence for the authorisation of innovative medicinal products[1].

The Clinical Trials Office (USC) has recently identified that requests are being submitted for the authorization of CTs that use and/or generate data deriving from the application of AI or ML models, or that are designed or managed through the application of such models and, therefore, are impacted by them. However, the application of AI or ML models shows some criticalities when it comes to the current regulatory framework that applies to clinical trials. Such criticalities emerge when AI or ML models do not correctly fit in that regulatory framework or if the associated risks are not adequately and preliminarily discussed and assessed.
In terms of risks, the following can be mentioned, by way of example: the new methods or techniques have not been fully validated; the reliability of the datasets cannot be guaranteed; the quality of the algorithms, the transparency and security of the clinical evidence generated cannot be ensured.

At European level, initiatives are underway to promote the innovation in the pharmaceutical field and to analyse its impact on the current standards and regulatory framework with the aim of facilitating the development of innovative solutions and making them available to patients. In this regard, the European Medicines Agency (EMA) is available to promote an early dialogue with developers through the Innovation Task Force (ITF) and the Scientific Advice Working Party (SAWP). The ITF is a multidisciplinary group, made up of experts from EMA and national regulatory agencies, whose purpose is to initiate an early dialogue on emerging therapies and technologies and borderline products, for which there is not yet a solid scientific experience and/or legislation. The SAWP, on the other hand, provides specific advice on innovative methods and tools for medicine development, including digital technologies[2].
The issues related to technological and scientific innovation are also investigated by the EU-Innovation Network (EU-IN), a joint European group by the Heads of Medicines Agencies (HMA) and the EMA, that is composed of the European Innovation Offices and the Innovation Task Force (ITF) of EMA. The purpose of the network is to support innovation in the early stages of the development of innovative medicines, products, technologies and processes, with an emphasis also on academia and small and medium-sized enterprises. The task of the EU-IN is, therefore, to address the regulatory issues concerning innovation, in order to boost research and, at the same time, make innovation available to patients in a timely manner, ensuring that regulatory requirements are met. Finally, in light of the need to implement an integrated and effective approach to innovation and early access to medicines, the INNO-Group initiative has been launched within the European

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[1] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions - Pharmaceutical Strategy for Europe - COM(2020) 761 final - 25.11.2020
[2] Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products - EMA/219860/2020 - Human Medicines Division – 1 June 2020

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network over the past three years. It is based on a constant and direct interaction with and on integrated discussions between the main working groups on innovation, research and access to medicines (SAWP, CTFG, EU-IN and EUnetHTA), with a shared approach to the management of emerging innovations. The aim is to identify the most efficient regulatory pathways that allow quick access to innovative therapeutic strategies.

At national level, AIFA promotes an early dialogue on innovation and is actively engaged in responding to the needs and challenges that this entails, with the aim of guaranteeing patients' access and use of technological innovations, in line with the European initiatives. Therefore, the Innovation & EMA Scientific Advice Office (UISA) meets the developers as part of innovation meetings, where issues regarding innovative products, technologies or processes are discussed across all competent Offices of the Agency.

Despite efforts to set up a global initiative on AI/ML in the European Union (EU)[3,4], there are many criticalities that the regulatory network still has to manage, in order to implement the digital transformation, also taking into account the slow pace at which regulatory processes are updated and the lack of regulatory standards, guidelines and criteria for the validation and use of patient health data, as well as AI and ML data[5].

Pending the adoption, by the competent EU and/or international bodies, of dedicated CT guidelines involving the use of AI or ML systems, the USC deems it necessary to outline the state of the art, with the aim of optimizing the submission of a request for authorization of CTs that already are impacted by AI/ML, recognizing their innovation, but at the same time, placing them in the regulatory framework currently in force and ensuring a positive benefit-risk profile for CTs subjects.

In order to achieve this goal, and building on the experience and collaboration among the Offices involved, AIFA has prepared this document, which is also the result of an interaction with some of the actors potentially involved in the evaluation and authorization process.

2. CONTENT WARNINGS

This document contains a collection of information, recommendations and references to standards, documents and publications, and represent a general guide, a useful tool for Sponsors to optimize the documentation supporting the submission of a request for authorization of CTs involving the use of AI or ML systems. It can be considered as a "living document", in that the information contained therein is potentially subject to continuous updates on the basis of new scientific findings and/or the publication of updated and dedicated guidelines and/or regulatory changes regarding the specific relevant subject.

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[3] Communication from the Commission to the European Parliament, the European Council, the Council, the European Economic and Social Committee and the Committee of the Regions - Artificial Intelligence for Europe - COM(2018) 237 final - 25.4.2018

[4] Proposal for a Regulation of the European Parliament and of the Council laying down harmonised rules on Artificial Intelligence (Artificial Intelligence Act) and amending certain Union legislative Acts on a European approach for Artificial Intelligence - COM(2021) 206 final - 21.4.2021

[5] European medicines agencies network strategy to 2025 - EMA/85501/2020

3. LIST OF ABBREVIATIONS

AI: Artificial Intelligence

AIFA: Italian Medicines Agency

CA: Competent Authority

CT: Clinical Trial

CTFG: Clinical Trials Coordination and Facilitation Group

DGDMF: Direzione Generale dei Dispositivi Medici e del servizio Farmaceutico

EMA: European Medicines Agency

EU: European Union

EU-IN: EU-Innovation Network

EUnetHTA: European Network for Health Technology Assessment

GDPR: General Data Protection Regulation

HMA: Heads of Medicines Agencies

IMP: Investigational Medicinal Product

ITF: Innovation Task Force

IVDR: In Vitro Diagnostic Medical Devices Regulation

MDR: Medical Devices Regulation

MDSW: Medical Device Software

ML: Machine Learning

MoH: Minister of Health

RWE: Real world evidence data

SAMD: Software as Medical Device

SAWP: Scientific Advice Working Party

UISA: Innovation & EMA Scientific Advice Office

USC: Clinical Trials Office

4. GUIDE TO THE SUBMISSION OF A CT INVOLVING AI/ML SYSTEMS

4.1 COVER LETTER FOR THE REQUEST FOR AUTHORISATION OF A CT

A CT can foresee the use of or be impacted by an AI model or ML technique.
In the event that the CT involves the use of AI or ML systems, this must be stated in the template "MODELLO DELLA LETTERA DI TRASMISSIONE PER LA DOMANDA DI AUTORIZZAZIONE ALLA SPERIMENTAZIONE CLINICA DI FASE … (I-II-III-IV)", available on AIFA's website at the following link: https://www.aifa.gov.it/modulistica-sperimentazione-clinica.

Furthermore, if the related information is not already available in the Protocol, in the event that one or more interactions between the SC and AI/ML are identified, it is necessary to provide detailed information for each of them regarding:

• The type of model and the level of interaction foreseen with the CT
• Whether the model is subject or not to clinical investigation in the context of the CT (e.g. correlation with the objectives and/or endpoints of the CT)
• The expected impact deriving from the use of the AI/ML system (e.g. rights, safety, well-being of subjects, data or results of the CT, etc…)

By way of example, some of the potential uses of AI/ML in the context of CTs are reported below:

• IMP discovery and development
• Protocol Design
• Conduction of CTs
• CT subject elegibility
• Adverse events reporting
• Medicinal product safety and toxicity
• Quality and data validation
• Quality assurance
• Real world evidence data (RWE)
• Clinical decision support
• Compliance to therapy
• Supply chain
• Application to wearables and app

In the event that the AI/ML systems are subject to clinical investigation in the context of CTs, for further information on the clinical trial involving medical devices, the *Ufficio 6 - Sperimentazione clinica dei dispositivi medici* of the *Direzione generale dei dispositivi medici e del servizio farmaceutico* (DGDMF) of the Minister of Health (MoH) should be contacted beforehand.

In general, for a software, and therefore also an AI/ML system, to qualify as a medical device, the following conditions must apply[6]:

1) it must be a software constituted by a set of instructions to process input data and create output data;
2) it must have a medical purpose in accordance with the provisions of Art. 2(1) of the MDR, such as diagnosis, prevention, monitoring, treatment, regardless of whether it is independent or participates in/influences the use of the device. The medical purpose is established by the manufacturer within the intended use of the device and must be confirmed by clinical evidence;
3) it must be directed to the benefit of a specific patient.

4.2 BENEFIT-RISK ASSESSMENT

If the rights, safety, well-being of the subjects participating in the trial, the data or results of the CT are impacted by an AI model or ML technique, a specific assessment of the benefit-risk associated with the use of the AI or ML model must be submitted, unless it is already available in the Protocol. The relevant information should be reported in the Informed Consent Form.

In addition, further data and information will need to be submitted[7,8,9,10] to support the AI/ML model, confirming also that the requirements for high-risk AI applications[11] and the ethical principles[12,13,14] are met. Such information includes, but is not limited to:

• The intended use of the model
• The purpose of the intended use and the related added value (and/or benefit for the subjects in the CT) deriving from the use of AI/ML
• Who the users are in the context of the CT (healthcare personnel, subjects in the CT, etc...)
• The type of model with the specification of the algorithm(s) used and of the version
• Any previous uses and the level of evidence of the quality of the studies used to build the model
• The type (including, for example, the original format of the data, whether they are structured or unstructured), the origin and method of acquisition of the data used, the reliability, security, standardization of the dataset(s), potential biases (representativeness of the data in terms of study population, therapeutic indication, gender, etc...) and how any missing

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[6] MDCG 2019-11-Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR

[7] Cruz Rivera S. et al. Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI extension. Nat Med. 2020 Sep;26(9):1351-1363. doi: 10.1038/s41591-020-1037-7

[8] Liu X. et al. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. Nat Med. 2020 Sep;26(9):1364-1374. doi: 10.1038/s41591-020-1034-x

[9] Vollmer S. et al. Machine learning and artificial intelligence research for patient benefit: 20 critical questions on transparency, replicability, ethics, and effectiveness. BMJ. 2020 Mar 20;368:l6927. doi: 10.1136/bmj.l6927

[10] Norgeot B. et al. Minimum information about clinical artificial intelligence modeling: the MI-CLAIM checklist. Nat Med. 2020 Sep;26(9):1320-1324. doi: 10.1038/s41591-020-1041-y

[11] White paper on Artificial Intelligence - A European approach to excellence and trust - COM(2020) 65 final 19.2.2020

[12] Ethics guidelines for trustworthy AI - High-Level Expert Group on Artificial Intelligence - 8 April 2019

[13] EU guidelines on ethics in artificial intelligence: Context and implementation - September 2019

[14] Intelligenza Artificiale e Medicina: Aspetti Etici – Comitato Nazionale per la Bioetica – Comitato Nazionale per la Biosicurezza le Biotecnologie e le Scienze della vita – 29 maggio 2020

and/or low quality data are managed (and/or a Data Management Plan including all the information)
• Reproducibility and transparency: the possibility and the methods to access the datasets and the model (by the CA, the subjects in the CT, the public, etc...)
• The expected output and the correlation with the objectives and endpoints of the CT
• Details about the training phase of the model (including for example the characteristics and independence of the training and of the test sets), the validation and performance of the model
• A Risk Assessment[15] (and/or a Risk Management Plan including all the information)
• If a decision support software is configured as a medical device, this condition should clearly be considered in a specific Risk Assessment and the Manufacturer should include in the technical documentation a detailed description of the algorithm, the involved datasets and the significant changes envisaged in the case of systems which, during operation, vary through learning
• Report the level of transparency of the data flow and of the results, and the interpretability by the CAs, indicating for example whether a method and/or tools are available for the interpretation of the results (another software or additional functionality of the AI model), or provide an explanation of how the algorithm works in making decisions, focusing on the demonstration and the confirmation that the system using AI/ML is safe and appropriate for the intended use[16]
• Information on the potential CE marking of the device
• Safety and performance characteristics of the device
• Ability to reproduce the results and to verify the external validity
• Compliance with the General Data Protection Regulation (GDPR)
• Data storage and cybersecurity
• Usability, data governance, hardware/interface requirements, etc…

4.3 REGULATORY FRAMEWORK

Before submitting a request for authorisation of a CT, it is necessary to evaluate the regulatory framework of the AI models or ML methods in advance, framing their use and assessment within the Italian and European regulatory framework in force, with the proper identification of the reference CA.

Please note that the CA for the clinical investigations of medical devices is the MoH. In addition, should the AI/ML system be classified as medical device software, the web pages dedicated to the clinical investigations of medical devices published on the MoH website should be consulted and the *Ufficio 6 - Sperimentazione clinica dei dispositivi medici* of MoH's DGDMF should be contacted in advance.

Also note that a specific category of medical device software is the Medication Decision Support Software, intended to be used by healthcare professionals to optimize a patient's therapeutic plan by identifying possible contraindications, possible interactions among various medicinal products and the need for dose adjustments.

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[15] Reflection paper on risk based quality management in clinical trials - EMA/269011/2013 - 18 November 2013
[16] Contribution to the discussion on the European Commission's Data Strategy and AI White Paper Report by the EIT Health Consultative Group, 31st May 2020

This software is used for disease prevention, monitoring, treatment or mitigation purposes and, therefore, should be considered a medical device[17].

To this end, some useful information is reported below.

Medical device software or decision support software

Document	Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR
Link	https://ec.europa.eu/docsroom/documents/37581/attachments/1/translations/en/renditions/native
Document	Manual on borderline and classification in the community regulatory framework for medical devices
Link	https://ec.europa.eu/docsroom/documents/35582/attachments/1/translations/en/renditions/native
Document	Infographic - Is your software a Medical Device?
Link	https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2021_mdsw_en.pdf
Document	Proposal for a Regulation Of The European Parliament And Of The Council Laying Down Harmonised Rules On Artificial Intelligence (Artificial Intelligence Act) And Amending Certain Union Legislative Acts
Link	https://eur-lex.europa.eu/legal-content/ES/TXT/?uri=COM:2021:206:FIN
Document	IMDRF/CYBER WG/N60FINAL:2020 Principles and Practices for Medical Device Cybersecurity
Link	http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-200318-pp-mdc-n60.pdf
Document	IMDRF/SaMD WG/N41FINAL:2017 Software as a Medical Device (SaMD): Clinical Evaluation
Link	http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170921-samd-n41-clinical-evaluation_1.pdf

4.4 TREATMENT OF PERSONAL DATA

It is recommended to focus on the legal basis for the processing of personal data in agreement with the current legislation.

To this end, some useful information is reported below.

General Data Protection Regulation (GDPR)

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[17] Manual on borderline and classification in the community regulatory framework for medical devices. Version 1.22 (05-2019)

Document	Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
Link	https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=EN

Document	The impact of the General Data Protection Regulation (GDPR) on artificial intelligence
Link	https://www.europarl.europa.eu/RegData/etudes/STUD/2020/641530/EPRS_STU%282020%29641530_EN.pdf

Document	Question and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation
Link	https://ec.europa.eu/health/sites/health/files/files/documents/qa_clinicaltrials_gdpr_en.pdf

Document	Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR) (art. 70.1.b))
Link	https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_opinionctrq_a_final_en.pdf

4.5 VALIDATION, CLINICAL EVALUATION, PERFORMANCE

The necessary documentation to certify validation, clinical evaluation and performance should be evaluated in advance.
To this end, some useful information is reported below.

Medical Device Coordination Group (MDCG) documents

Document	MDCG 2020-1 Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software March 2020
Link	https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020_1_guidance_clinic_eva_md_software_en.pdf

Standards for software development (for a complete list, further information and/or updates, consult the website https://www.iso.org/)

Document	ISO/UNI/IEC/EN (e.g. IEC 62304:2006: 'Medical device software - Software life cycle processes'; and relevant updates
Link	https://www.iso.org/

Document	EC 80002-1:2009 Medical Device Software - Part1: guidance on the application of ISO 14971:2007 with reference to IEC 62304
Link	https://www.iso.org/

Document	IEC 80001-1 Risk management aspects
Link	https://www.iso.org/

Document	EC 82304-1:2016 Health software – Part1: General requirements for product safety
Link	https://www.iso.org/

Note	A new standard ISO/AWI TS 82304-2. Health software - Part 2: Health and wellness apps—Quality and reliability is under development.
Link	https://www.iso.org/

4.6 CYBERSECURITY

The management of IT security should be evaluated in advance.
To this end, some useful information is reported below.

Document	MDCG 2019-16 Guidance on Cybersecurity for medical devices
Link	https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_cybersecurity_en.pdf

4.7 DATASET & BIG DATA

The management of datasets, and the data format used should be evaluated in advance.
To this end, some useful information is reported below.

Document	HMA/EMA Joint Task Force on Big Data – Interim (Phase I) report
Link	https://www.ema.europa.eu/en/documents/minutes/hma/ema-joint-task-force-big-data-summary-report_en.pdf

Document	HMA-EMA Joint Big Data Taskforce Phase II report: 'Evolving Data-Driven Regulation'
Link	https://www.ema.europa.eu/en/documents/other/hma-ema-joint-big-data-taskforce-phase-ii-report-evolving-data-driven-regulation_en.pdf

4.8 INSTITUTIONAL WEBSITE OF THE MINISTRY OF HEALTH

Institutional webpage	For further information on clinical trials of medical devices, it is recommended to contact the *Ufficio 6 - Sperimentazione clinica dei dispositivi medici* of the MoH's DGDMF
Link	http://www.salute.gov.it/portale/ministro/p4_5_2_4_2.jsp?lingua=italiano&menu=uffCentrali&label=uffCentrali&id=1229

4.9 OTHER INFORMATION

Document	Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)
Link	https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-and-Machine-Learning-Discussion-Paper.pdf
Document	White paper from COCIR related to AI in the EU Medical device legislation
Link	https://www.cocir.org/fileadmin/Position_Papers_2020/COCIR_Analysis_on_AI_in_medical_Device_Legislation_-_Sept._2020_-_Final_2.pdf

5. CONTACTS

It is possible to contact AIFA for CTs related questions at the following e-mail address: sperimentazione.clinica@aifa.gov.it

6. ACKNOWLEDGMENTS

We wish to thank, for their support and collaboration, all those people with whom the document has been shared for consultation and review.

ANNEX I

CT & AI/ML GENERAL SUBMISSION WORKFLOW

As a support in the submission process of a CT that is impacted by AI/ML, a general submission workflow is proposed. This example is provided to suggest reflections on a limited number of potential scenarios, and it is not intended to exhaustively cover all possible settings.

Start of CT submission workflow

Potential Fields of Interaction

IMP discovery & development
Protocol Design
Study conduction
Decision making
Patient elegibility
Drug safety & toxicity
Real word evidence data
QA & AE reporting
Data quality & validation
Other...

Any use of AI/ML? — NO → No further action, proceed with CT submission.

YES

Document → Provide related information in the CT submission cover letter, and/or in the Protocol as applicable.

Example of related information

The type of model and the level of interaction foreseen with the CT.
If the model is or is not object of study in the context of the CT (e.g. correlation with the objectives and/or endpoints).
The anticipated impact of the use of the AI/ML system (on rights, safety and well-being of trial subjects, data or results of the CT, etc...).

Is AI/ML a MDSW or object of study in the context of the CT? (e.g. correlation with the objectives and/or endpoints). — NO → Are rights, safety and well-being of trial subjects, data or results of the CT impacted by AI/ML? — NO → No further action, proceed with CT submission. No additional AI/ML related information expected.

YES

Regulatory framework check. Consult also the medical device Competent Authority for further processing.

AND

YES → Provide dedicated Benefit-Risk assessment. (Document)

Example of supporting data

Validation of methods/techniques, performance
Access, standardization and quality of data sets
Transparency of algorithms
Compliance with GDPR
Quality of clinical evidence generated
Etc...

AI/ML supporting data should be submitted in the CT application.

In general, these are computer based tools which combine 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 treatment of individual patients.

The software is intended to be used for the purpose of prevention, monitoring, treatment or alleviation of a disease and should therefore be qualified as a medical device.

Is AI/ML a decision support software? — NO → No further action, proceed with CT submission. No additional AI/ML related information expected.

YES

If AI/ML is a decision support software, provide specific Risk assessment, description of algorithm, datasets and significant changes expected during learning. (Document)

Example of supporting data

Level of transparency in data flow and results
Availability of methods/tools for the interpretation of results
Explanation of how the algorith works in taking decisions
Demonstration and confirmation that the model is safe and adequate for the inteded use
Etc...

Additional AI/ML supporting data should be submitted in the CT application.

AND → Proceed with CT submission.

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ANNEX II

CASE STUDIES

According to requests for authorisation of CTs received at the USC, foreseeing the use of AI/ML in CTs, we are reporting hereby a few Case Studies illustrating potential scenarios, in order to share information and optimize the CT assessment process.
Please note that these scenarios are merely examples and do not cover all possibilities, which should be evaluated individually.

CASE STUDY 1

AI/ML: A supercomputing platform (AI) was utilized to find several promising molecules able to support treatment of condition-1. Among these molecules, IMP1 was found as a promising molecule to treat condition-1 with a dual activity. IMP1 has a Marketing Authorisation (MA) for indication-0.

Protocol: The aim of the clinical trial is to assess the efficacy of two different doses of IMP1 for preventing the evolution of condition-1 towards severe and critical disease.

Discussion: AI/ML was used in order to select the IMP. IMP1 has previously obtained a MA for indication-0. Additional safety and non clinical data may be necessary due to the use of IMP1 for the treatment of condition-1 not covered by the MA for indication-0. However, there is no direct impact on the rights, safety and well being of trial subjects, data or results of the CT, due to the use of AI/ML only in the selection of the best molecule for treatment of condition-1. Therefore, relevant data and details of the AI model are not expected to be discussed in the clinical trial application.

Case Study 1 – CT & AI/ML Submission Workflow

Start of CT submission workflow

Potential Fields of Interaction

IMP discovery & development

Any use of AI/ML? —NO→ No further action, proceed with CT submission.

YES

Document → **Provide related information in the CT submission cover letter, and/or in the Protocol as applicable.**

Example of related information

The type of model and the level of interaction foreseen with the CT.
If the model is or is not object of study in the context of the CT (e.g. correlation with the objectives and/or endpoints).
The anticipated impact of the use of the AI/ML system (on rights, safety and well-being of trial subjects, data or results of the CT, etc...).

Is AI/ML a MDSW or object of study in the context of the CT? (e.g. correlation with the objectives and/or endpoints). —NO→ **Are rights, safety and well-being of trial subjects, data or results of the CT impacted by AI/ML?** —NO→ **No further action, proceed with CT submission. No additional AI/ML related information expected.**

YES

YES

Regulatory framework check. Consult also the medical device Competent Authority for further processing.

AND

Document → Provide dedicated Benefit-Risk assessment.

Example of supporting data

Validation of methods/techniques, performance
Access, standardization and quality of data sets
Transparency of algorithms
Compliance with GDPR
Quality of clinical evidence generated
Etc...

AI/ML supporting data should be submitted in the CT application.

In general, these are computer based tools which combine 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 treatment of individual patients.

The software is intended to be used for the purpose of prevention, monitoring, treatment or alleviation of a disease and should therefore be qualified as a medical device.

Is AI/ML a decision support software? —NO→ No further action, proceed with CT submission. No additional AI/ML related information expected.

YES

If AI/ML is a decision support software, provide specific Risk assessment, description of algorithm, datasets and significant changes expected during learning.

Example of supporting data

Level of transparency in data flow and results
Availability of methods/tools for the interpretation of results
Explanation of how the algorith works in taking decisions
Demonstration and confirmation that the model is safe and adequate for the inteded use
Etc...

Additional AI/ML supporting data should be submitted in the CT application.

Document →

AND → Proceed with CT submission.

CASE STUDY 2

AI/ML: An AI model has been built based on a standardized ML platform that also includes other algorithms and Deep Learning. Based on a retrospective analysis on a specific population, the results will serve to build an AI-based computational framework identifying potential prognostic biomarkers and molecular predictors of therapeutic response.

In the prospective part of the project, the AI model has been adopted to analyze the subject profile in order to identify good or poor responders to therapy in a prospective CT study, with the same population.

Protocol: The primary objective of the study is the assessment of the efficacy of the AI model. The allocation to the best treatment option is performed following the indication of each subject's profile as resulted from the computational framework platform based on AI. The AI guide the Investigator to choose the best therapy based on a personalized medicine approach.

Discussion: The objective of the study is not related to the safety/efficacy of the IMP but focus on the efficacy of the AI. The study cannot be assessed under the legal basis of Directive 2001/20/EC, as transposed into the Italian Decreto Legislativo 24 giugno 2003, n. 211.

Note: Even in the case the AI/ML was not object of study in the context of the CT, it would be nevertheless used to select the best treatment option for a subject to be allocated in the CT, this would be therefore classified as a clinical decision support software.

Medical device regulatory framework needs to be consulted and medical device Competent Authority should be contacted.

Case Study 2 – CT & AI/ML Submission Workflow

Start of CT submission workflow

Potential Fields of Interaction

Decision making

Any use of AI/ML? — NO → No further action, proceed with CT submission.

Example of related information

The type of model and the level of interaction foreseen with the CT.
If the model is or is not object of study in the context of the CT (e.g. correlation with the objectives and/or endpoints).
The anticipated impact of the use of the AI/ML system (on rights, safety and well-being of trial subjects, data or results of the CT, etc...).

YES — Document → **Provide related information in the CT submission cover letter, and/or in the Protocol as applicable.**

Is AI/ML a MDSW or object of study in the context of the CT? (e.g. correlation with the objectives and/or endpoints). — NO → **Are rights, safety and well-being of trial subjects, data or results of the CT impacted by AI/ML?** — NO → No further action, proceed with CT submission. No additional AI/ML related information expected.

YES

Regulatory framework check. Consult also the medical device Competent Authority for further processing.

AND

YES → Document → **Provide dedicated Benefit-Risk assessment.**

Example of supporting data

Validation of methods/techniques, performance
Access, standardization and quality of data sets
Transparency of algorithms
Compliance with GDPR
Quality of clinical evidence generated
Etc...

AI/ML supporting data should be submitted in the CT application.

In general, these are computer based tools which combine 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 treatment of individual patients.

The software is intended to be used for the purpose of prevention, monitoring, treatment or alleviation of a disease and should therefore be qualified as a medical device.

Is AI/ML a decision support software? — NO → No further action, proceed with CT submission. No additional AI/ML related information expected.

YES → Document → **If AI/ML is a decision support software, provide specific Risk assessment, description of algorithm, datasets and significant changes expected during learning.**

Example of supporting data

Level of transparency in data flow and results
Availability of methods/tools for the interpretation of results
Explanation of how the algorith works in taking decisions
Demonstration and confirmation that the model is safe and adequate for the inteded use
Etc...

Additional AI/ML supporting data should be submitted in the CT application.

AND → **Proceed with CT submission.**