AI-based medical devices: the applicable law in the European Union

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AI-BASED MEDICAL DEVICES: THE APPLICABLE LAW IN THE EUROPEAN UNION

ABSTRACT: Digital health refers to the application of various technologies with the aim of supporting/offering healthcare services. Among such technologies, AI poses new regulatory challenges. This article aims at clarifying, in the light of the EU legislation, whether such technologies shall be considered medical devices, and which law applies to the various phases of their lifecycle. In this regard, the provisions of the relevant pieces of EU legislation (the Medical Device Regulation, the legislation on clinical trials of medicines, and the recent Commission's proposal for an AI Act) will be coordinated, to identify the rules applicable to AI-based MDs overall and the requirements that the economic actors involved in their lifecycle shall comply with.

KEYWORDS: AI; medical devices; digital health; digital medicine; digital therapeutics; EU; AFSJ

SUMMARY: 1. Introductory Remarks – 2. Methodology – 3. AI and healthcare: concepts and examples – 4. The Medical Device Regulation (MDR) 2017/745/EU – 4.1. The definition of medical device and its classification – 4.2. The main subjects involved in the lifecycle of a MD and their obligations – 4.3. The clinical evaluation and the clinical investigation – 5. The legislation on clinical trials of medicines for human use and its relevance to AI-MDs – 5.1. Does CTR apply to AI-MDs? – 5.2. Clinical trials: the procedure – 6. The European Medicines Agency (EMA) and the AI-MDs – 7. The Commission's Proposal for an Artificial Intelligence Act (AIA) – 7.1. The Explanatory Memorandum and the Communication from the European Commission *"Fostering a European approach to Artificial Intelligence"* – 7.2. The Proposal – 8. Conclusive remarks.

1. Introductory Remarks

The advances in technology, especially in the field of artificial intelligence (AI), have deeply affected several sectors, including healthcare.[1]

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[1] Namely, "healthcare" in a broad sense, namely consisting of many fields of science, from pharmaceuticals to medicine. As for the role of AI in pharmaceuticals, particularly in the drug discovery process, see ex multis J.L. KRAUS, *Can artificial intelligence revolutionize drug discovery?*, in *AI & Society*, 35, 2, 2020, 501-504, https://doi-org.ezp.biblio.unitn.it/10.1007/s00146-019-00892-0. Concerning the impact of AI on the doctor-patient relationship, see B. MITTELSTADT, *THE IMPACT OF ARTIFICIAL INTELLIGENCE ON THE DOCTOR-PATIENT RELATIONSHIP*. *Report commissioned by the Steering Committee for Human Rights in the fields of Biomedicine and Health* (CDBIO) – *Council of Europe*, December 2021, available at https://www.coe.int/en/web/bioethics/report-impact-of-ai-on-the-doctor-patient-relationship (last access 17/07/2022).

The topic of digital health has been widely assessed by the literature: it refers to the application of various technologies with the aim of supporting and/or offering healthcare services. Among these technologies, the following may be mentioned: telemedicine, apps, wearable devices, smartphones, digital therapeutics. Although a standard-vocabulary has not yet been developed by specialists, one can classify the wide range of such technologies into three macro-categories: *a)* Digital Health; *b)* Digital Medicine; and *c)* Digital Therapeutics.

Digital Health (*alias* eHealth) encompasses technologies – such as apps or web apps – that support users in modifying their lifestyle, for wellness and health-related purposes. For instance, the following products can be mentioned: fitness trackers or scheduling apps, health information technologies (HIT) like electronic medical records systems, as well as telemedicine platforms.[2]

Digital Medicine includes software and/or hardware products, developed upon clinical evidence, that permit medical treatments, *e.g.*, digital biomarkers, remote patient monitoring tools, and decision support tools.[3]

Digital Therapeutics (*alias* DTx) refers to technologies that allow therapeutical operations – *i.e.*, the prevention, the management, or the treatment of medical disorders or diseases – by means of high-quality software, which are based on scientific evidence obtained through rigorous clinical investigations.[4]

Basically, this article aims at investigating two questions. In the first place, the aforementioned technologies' legal nature under the EU law will be examined, in order to clarify whether they shall be considered medical devices (MDs). In the second place, the norms applicable to the various phases of their development, commercialisation, and application need to be illustrated. Particularly, the provisions of the relevant pieces of EU legislation – *i.e.*, the Medical Device Regulation (MDR) EU/2017/745,

[2] See *inter alia* N.R. Grossi, B. Batinic, S. Moharitsch, *Sleep and Health: Examining the Relation of Sleep to Burnout and Well-Being Using a Consumer Fitness Tracker*, in *Health and Technology*, 11, 6, 2021, 1247-1257, https://doi.org/10.1007/s12553-021-00603-0; K.D. Wowak, S. Handley, K. Kelley, C.M. Angst, *Strategic Sourcing of Multicomponent Software Systems: The Case of Electronic Medical Records*, in *Decision Sciences*, 2022, 1-18, https://doi.org/10.1111/deci.12576; A.J. Gadzinski, J.L. Gore, C. Ellimoottil, A.Y. Odisho, K.L. Watts, *Implementing Telemedicine in Response to the COVID-19 Pandemic*, in *Journal of Urology*, 204, 1, 2020, 14-16, https://doi.org/10.1097/JU.0000000000001033.

[3] See *inter alia* Y. Rykov, T.Q. Thach, I. Bojic, G. Christopoulos, J. Car, *Digital Biomarkers for Depression Screening With Wearable Devices: Cross-Sectional Study With Machine Learning Modeling*, in *JMIR MHealth and UHealth*, 9, 10, 2021, e24872, https://doi.org/10.2196/24872; A.C. Cuțitoi, *Remote Patient Monitoring Systems, Wearable Internet of Medical Things Sensor Devices, and Deep Learning-Based Computer Vision Algorithms in COVID-19 Screening, Detection, Diagnosis, and Treatment*, in *American Journal of Medical Research*, 9, 1, 2022, 129-144, https://doi.org/10.22381/ajmr9120229; D. Stone, L. Michalkova, V. Machova, *Machine and Deep Learning Techniques, Body Sensor Networks, and Internet of Things-Based Smart Healthcare Systems in COVID-19 Remote Patient Monitoring*, in *American Journal of Medical Research*, 9, 1, 2022, 97-112, https://doi.org/10.22381/ajmr9120227; L. Lapp, K. Egan, L. McCann, M. Mackenzie, A. Wales, R. Maguire, *Decision Support Tools in Adult Long-Term Care Facilities: Scoping Review*, in *Journal of Medical Internet Research*, 24, 9, 2022, e39681, https://doi.org/10.2196/39681.

[4] See *inter alia* G. Trifirò, S. Crisafulli, G. Puglisi, G. Racagni, L. Pani, *Terapie digitali come farmaci*, in G. Gussoni (ed.), *Terapie digitali, una opportunità per l'Italia*, in *Tendenze nuove*, Special Issue 1, 2021, 147-148, available at http://www.tendenzenuove.it/2021/01/13/terapie-digitali-come-farmaci/ (last access 17/07/2022); G. Recchia, M.D. Capuano, N. Mistri, R. Verna, *Digital Therapeutics-What they are, what they will be*, in *Acta Scientific Medical Sciences*, 4, 3, 2020, 1-9, https://actascientific.com/ASMS/pdf/ASMS-04-0575.pdf (last access 17/07/2022).

the legislation on clinical trials of medicines for human use, and the recent Commission's proposal for an AI Act – can be coordinated, to identify the rules applicable to AI-based MDs overall (a '*reductio ad unum*') and the requirements that the economic actors involved in their lifecycle shall comply with.

2. Methodology

The study will be conducted, first of all, by separately analysing the aforementioned pieces of EU legislation, with special attention those provisions resulting relevant to matter of AI medical devices. In particular, the Medical Device Regulation (MDR) 2017/745/EU will be analysed in Paragraphs 4 to 4.3, the legislation on clinical trials of medicines for human use and its relevance to AI-MDs will be review in Paragraphs 5 to 6, and the European Commission's Proposal for an AI Act will be examined in Paragraphs 7 to 7.2.
Then, in the conclusive remarks (Paragraph 8), the requirements provided for in the various analysed acts will be coordinated, to clarify the law applicable overall in case of development, commercialisation, and application of an AI-based MD.

3. AI and healthcare: concepts and examples

Two main approaches relate to AI, *i.e.*, model-based and machine learning (ML)-based AI.[5]
In model-based AI, the system imitates the behaviours of experts on a given domain, such as the healthcare sector. By way of example, the programmer, with the help from healthcare specialists, defines the knowledge representation concerning a phenomenon (*e.g.*, myocardial infarction), and integrates such model into the system. Then, the AI 'treats' such phenomenon (*e.g.*, by assessing the risk-factor to which a patient is exposed, and by analysing the myocardial infarction's probability accordingly).[6]
There are two types of model-based AI:

a) systems that are based upon 'if-then rules,' in which, given the premise α, the AI formulates the conclusion β, to solve the question γ that has been posed by the programmer; and
b) systems that are based on the so-called 'trees,' in which the knowledge is organised by reference to a model that evokes the shape of an ideal tree, whose 'fronds' correspond to the different data-classification's alternatives, in such a way that, after the 'ramification,' an output is produced. In short, the AI recognises the question γ by virtue of a series of variables, that is, given the starting situation α, the various possible alternatives 'ramify' until the conclusion β is reached.

ML-based AI, instead, allows to realize more complex knowledge representations, by way of statistics and the probability theory. It is grounded on three learning methods.[7]

[5] On this argument, see *inter alia* P. TRAVERSO, *Breve introduzione tecnica all'intelligenza artificiale*, in *DPCE Online*, 51, 1, 2022, 155-67, available at http://www.dpceonline.it/index.php/dpceonline/article/view/1565 (last access 17/07/2022).
[6] See, *inter alia*, R. LIU, M. WANG, T. ZHENG, R. ZHANG, N. LI, Z. CHEN, H. YAN, Q. SHI, *An Artificial Intelligence-Based Risk Prediction Model of Myocardial Infarction*, in *BMC Bioinformatics*, 23, 1, 2022, 217, https://doi.org/10.1186/s12859-022-04761-4.
[7] In argument, see S.J. RUSSELL, P. NORVIG, *Artificial Intelligence. A Modern Approach*, Hoboken, 2021, 653-656.

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a) In the supervised learning, the programmer 'trains' the system by defining a set of expected outcomes in relation to a certain input range, and by constantly evaluating the achievements of the objectives (that is, the AI formulates a hypothesis, and every time it makes a mistake, such hypothesis is reviewed).[8]

b) The unsupervised learning, where the programmer provides for neither expected results nor error-reports, is usually applied for the so-called 'clustering,' that is, the formation of sets that include elements presenting analogies or relevant connections, *e.g.*, articles from a medical review concerning the same question.[9]

c) In the reinforcement learning, the system is led by a reward-punishment mechanism, *i.e.*, feedback messages.[10]

In ML the focus is not on the definition of a knowledge model (like the model-based AI), but on the collection of data and their inclusion within a training set. Such data allow the training of the computational models, for example the 'artificial neural nets' (ANNs).

ANNs (see Figure 1) are computational systems that are inspired by the functioning of the human brain, that is, the biological neural nets (BNNs). They are composed of some 'layers,' which in fact are parametric functions, *i.e.*, functions in which the parameters are not defined. Like the BNNs, ANNs' building blocks are highly interconnected computational tools. Also, they consist in computing networks that are distributed in parallel and function like the varying synaptic strengths of BNNs. In short, many input signals are sent to neurons, and the impact of each input is affected by the weight given to it. Eventually, the output signal depends on the summation block, which adds all the weighted inputs algebraically.

By way of example, among the other things, ANNs can be applied in melanoma diagnosis, to analyse images of moles (image recognition).[11] In this case, the task of the first layer of neurons (the blue balls) is to translate, in the form of numbers, data representing the pixels' colours. As the various neurons are connected to each other, the last layer of neurons (the red balls) does have the task to recognise melanoma, in such a way that, by virtue of statistical analysis grounded on the weight of each

[8] H.H. Rashidi, N. Tran, S. Albahra, L.T. Dang, *Machine Learning in Health Care and Laboratory Medicine: General Overview of Supervised Learning and Auto-ML*, in *International Journal of Laboratory Hematology*, 43, S1, 2021, 15-22, https://doi.org/10.1111/ijlh.13537.

[9] G. Vishnuvarthanan, M.P. Rajasekaran, P. Subbaraj, A. Vishnuvarthanan, *An Unsupervised Learning Method with a Clustering Approach for Tumor Identification and Tissue Segmentation in Magnetic Resonance Brain Images*, in *Applied Soft Computing*, 38, 2016, 190-212, https://doi.org/10.1016/j.asoc.2015.09.016.

[10] A.M. Rahmani, E. Yousefpoor, M.S. Yousefpoor, Z. Mehmood, A. Haider, M. Hosseinzadeh, R. Ali Naqvi, *Machine Learning (ML) in Medicine: Review, Applications, and Challenges*, in *Mathematics*, 9, 22, 2021, 2970, https://doi.org/10.3390/math9222970; S.H. Oh, S.J. Lee, J. Park, *Precision Medicine for Hypertension Patients with Type 2 Diabetes via Reinforcement Learning*, in *Journal of Personalized Medicine*, 12, 1, 2022, 87, https://doi.org/10.3390/jpm12010087.

[11] K. Das, C.J. Cockerell, A. Patil, P. Pietkiewicz, M. Giulini, S. Grabbe, M. Goldust, *Machine Learning and Its Application in Skin Cancer*, in *International Journal of Environmental Research and Public Health*, 18, 24, 2021, 13409, https://doi.org/10.3390/ijerph182413409; see also O.T. Jones, R.N. Matin, M. van der Schaar, K. Prathivadi Bhayankaram, C.K.I. Ranmuthu, M.S. Islam, D. Behiyat, R. Boscott, N. Calanzani, J. Emery, H.C. Williams, F.M. Walter, *Artificial Intelligence and Machine Learning Algorithms for Early Detection of Skin Cancer in Community and Primary Care Settings: A Systematic Review*, in *The Lancet Digital Health*, 4, 6, 2022, e466-e476, https://doi.org/10.1016/S2589-7500(22)00023-1.

connection, the probability of the correspondence between the images of moles and the presence of melanoma can be calculated.

The so-called deep learning (DL) is an interesting case of ML (see Figure 2). In DL-ANNs, many intermediate layers of neurons are 'hidden' (the green balls) and the programmer's training is aimed at defining such parameters. For instance, through the technique of 'back-propagation' (or 'backprop'), the programmer 'teaches' the output to the AI, by defining each intermediate layer's parameters backward, until the first level (the input) is reached. In the case of melanoma diagnosis, the programmer can teach the AI the features of skin cancer, in a way that the system recognises it.[12]

Figure 1 – Machine Learning

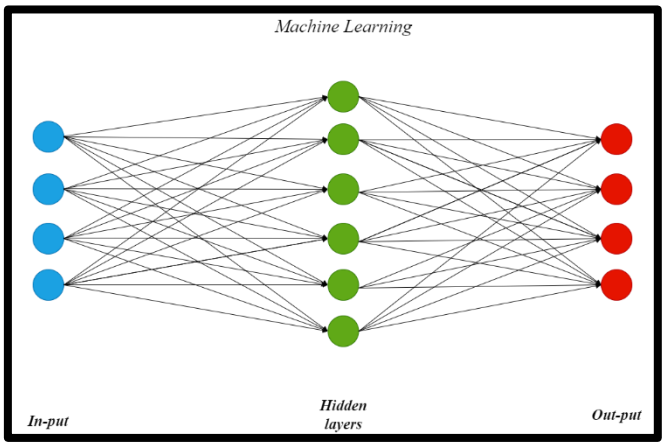
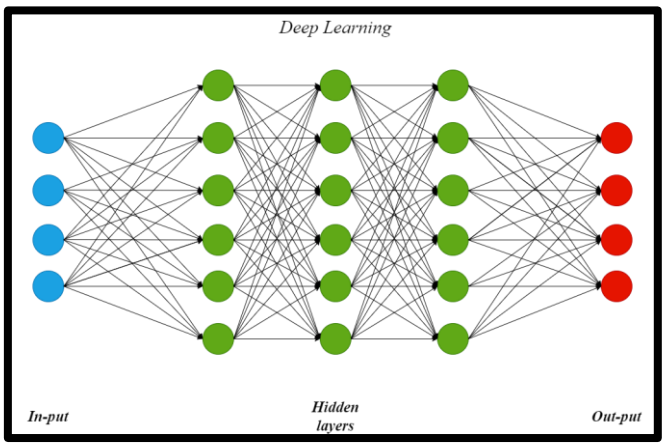


Figure 2 – Deep Learning



4.The Medical Device Regulation (MDR) 2017/745/EU

In the EU, the new Medical Device Regulation (MDR) 2017/745/EU (applicable from the 26th of May 2021) now governs the matter of medical devices (MDs). MDR replaced the Medical Device Directive (MDD) 93/42/ECC and the Active Implantable Medical Device Directive (AIMDD) 90/385/ECC.

[12] P. TRAVERSO, *op. cit.*, 163.

In general, the MDR does not remove any requirement provided for in the replaced pieces of legislation. Rather, it adds new ones, emphasising a lifecycle approach to safety of MDs.
Concisely, the major changes that the entry into force and the application of the MDR bring to the field of MDs are the following: *a)* the MDR tightens controls to ensure the safety and effectiveness of devices; *b)* the mechanism based upon the equivalence to already existing devices and allowing an accelerated placing on market or putting into service of devices, is no longer possible for all MDs; and *c)* the post-market clinical follow-up is extended to all MDs. All these requirements will increase the importance and the number of clinical evaluations and clinical investigations.[13]

4.1 The definition of medical device and its classification

As for the topic of this article, one should point out the definition of MD, which now encompasses (among other things) any software, intended by the manufacturer to be used, alone or in combination, for human beings for one or more specific medical purposes, including prediction and prognosis (see *amplius* Article 2.1). In this regard, one should distinguish MD-software on the one hand, encompassing tools that can be mainly classified within the abovementioned categories of Digital Medicine and Digital Therapeutics, and lifestyle/wellbeing-software on the other, falling into the category of eHealth. Indeed, only the former shall meet the requirements provided for in the MDR (see Recital 19). Additionally, it is debatable whether lifestyle/wellbeing-software fall within the scope of any specific safety and performance regulations at all, since they are unlikely to be governed by the General Product Safety Directive (GPSD).[14]
Hence, whether a device, including an AI one, is a MD under the MDR depends upon two fundamental elements, *i.e.*, the objective element of (at least) one of the medical purposes enlisted in Article 2(1), and the subjective element of the manufacturer's intent to produce a device with such a purpose.
Such conclusion is confirmed by the MEDDEV guidance 2.1/6 on the qualification and classification of standalone software used in healthcare,[15] even if it is prior to the entry into force of the MDR and refers to the MDD.[16]

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[13] N. Martelli, D. Eskenazy, C. Déan, J. Pineau, P. Prognon, G. Chatellier, M. Sapoval, O. Pellerin, *New European Regulation for Medical Devices: What Is Changing?*, in *CardioVascular and Interventional Radiology*, 42, 9, 2019, 1272-1278, https://doi.org/10.1007/s00270-019-02247-0; see also A. Migliore, *On the new regulation of medical devices in Europe*, in *Expert Review of Medical Devices*, 14, 12, 2017, 921-923, https://doi.org/10.1080/17434440.2017.1407648; S. Bianco, A. Nunziata, G. Pozzoli, *Clinical Investigation on Medical Devices, after the New European Regulation (2017/745)*, in *Clinical Trials and Practice. Open Journal*, 1, 1, 2017, 10-14, http://dx.doi.org/10.17140/CTPOJ-1-102.

[14] M.K. Sheppard, *mHealth: Disruptive Innovation, Regulation, and Trust – A Need for Balance*, in *Medical Law Review*, 28, 3, 2020, 549-572, https://doi.org/10.1093/medlaw/fwaa019.

[15] European Commission, *Guidelines on the Qualification and Classification of Standalone Software Used in Healthcare Within the Regulatory Framework of Medical Devices*, MEDDEV 2.1/6, July 2016, available at https://ec.europa.eu/health/document/download/c4c4d28f-0cc2-4604-ac86-0826d2938b17_en (last access 17/07/2022).

[16] Notwithstanding the nature of MEDDEV, *i.e.*, a guidance, at least one argument can be mentioned to affirm that, in effect, it provides for legal principles. In fact, in the *Snitem* case [European Court of Justice, case C-329/16, *Syndicat national de l'industrie des technologies médicales (Snitem) and Philips France v. Premier ministre and Ministre des Affaires sociales et de la Santé*, the 7th of December 2017], the ECJ, in the first place, reaffirmed some principles previously stated in the *Brain Products* case [European Court of Justice, case C-219/11, *Brain*

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In the light of Title 4 of MEDDEV, a software can be composed of a number of modules, each with its own purpose. When some modules satisfy the conditions to be treated as MD, while others not, only the former must carry the CE marking and comply with the requirements of the MD legislation. Furthermore, it is clearly stated that it is the obligation of the manufacturer to identify the boundaries and the interfaces of the different modules. The manufacturer should also identify the boundaries of the modules which fall within the scope of the MD legislation having regard to the intended use. In case of combination of modules falling within the scope of such legislation and modules of the whole software structure, other devices or equipment, the whole combination, including the connection system, must be safe and must not impair the specified performances of the MD modules.[17]

Pursuant to Article 51(1) MDR, MDs are classified into four main classes I, IIa, IIb, and III, depending on their intended purpose and their inherent risks,[18] in the light of the criteria enshrined in Annex VIII.[19] In general, class I encompasses most of the non-invasive and non-active devices, *i.e.*, the least risky ones; class IIa devises are of medium risk; class IIb devices are of medium/high risk; and class III refers to high risk-devices.

In particular, as for the software, it is classified as class IIa, where intended to provide information which is used to take decisions with diagnosis or therapeutic purposes, unless such decisions have an impact that may cause death or an irreversible deterioration of a person's state of health (in which case it is classified as class III), or a serious deterioration of a person's state of health or a surgical intervention (in which case it is classified as class IIb). Also, when intended to monitor physiological processes, a software is classified as class IIa, unless it is intended for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient (in which case it is classified as class IIb). All other software is classified as class I (see Rule 11 of Annex VIII).[20] From this perspective, however, one should consider that, with regards to AI-based MDs, it is implausible that the risk-class I can be of some relevance.

Products GmbH v. BioSemi VOF e altri, the 22nd of November 2012], especially that software constitutes a MD only when satisfying two cumulative conditions, namely the objective and subjective element mentioned above. In the second place, the Court determined that, when qualifying as a MD, a software "must […] compulsorily bear the CE marking of conformity when it is placed on the market". Then, "[o]nce the marking has been obtained, the product […] may be placed on the market and circulate freely in the European Union without having to undergo any additional procedure". In this regard, the Court explicitly refers to the interpretation provided for in the MEDDEV guidelines, as they mainly indicate that a software constitutes a MD where it is intended to create or modify medical information, in particular by means of calculation, quantification or comparison of the recorded data against certain references, in order to provide information about a particular patient. Hence, it can be maintained that the ECJ, by means of such reference, elevated the nature of MEDDEV 2.1/6, *i.e.*, from mere guidelines to legal principles. On this matter, see also T. MINSSEN, M. MIMLER, V. MAK, *When Does Stand-Alone Software Qualify as a Medical Device in the European Union? — The Cjeu's Decision in Snitem and What it Implies for the Next Generation of Medical Devices*, in *Medical Law Review*, 28, 3, 2020, 615-624, https://doi.org/10.1093/medlaw/fwaa012.

[17] M.K. SHEPPARD, *op. cit.*, 562-563.

[18] Pursuant to Article 2(23) MDR, for the purpose of the Regulation, 'risk' "means the combination of the probability of occurrence of harm and the severity of that harm".

[19] N. MARTELLI, D. ESKENAZY, C. DÉAN, J. PINEAU, P. PROGNON, G. CHATELLIER, M. SAPOVAL, O. PELLERIN, *op. cit.*, 1273.

[20] In this regard, see *amplius* MEDICAL DEVICE COORDINATION GROUP (MDCG), *Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR*, 11/10/2019,

Manufacturers of class I MDs other than custom-made or investigational devices, after having drawn up the technical documentation set out in Annexes II and III MDR, shall simply declare by themselves the conformity of their products. Instead, as for classes IIa, IIb and III devices (*i.e.*, presumably almost all the software as a MD),[21] a notified body (NB) must be involved (see Article 53 MDR).
Also, the Commission's *Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices* of 2019[22] needs to be mentioned: in particular, in Chapter 9, entirely dedicated to software and mobile applications, the fundamental role of MEDDEV 2.1/6 is reaffirmed, and twelve borderline categories of software and mobile applications are assessed.[23]

4.2 The main subjects involved in the lifecycle of a MD and their obligations

It can be useful to properly identify, in the light of the definitions provided for in MDR, the main subjects involved in the lifecycle of a MD, before pointing out their own obligations: *a)* the manufacturer;[24] *b)* the authorised representative;[25] *c)* the importer;[26] *d)* the distributor;[27] and *e)* the user.[28]
One should pay special attention to the obligations of manufacturers (see Article 10 MDR), whose intent to produce a device (also where AI-based) with a medical purpose – as we have clarified above – is crucial to qualify it as a MD. Such obligations can be summarised by means of three terms.[29]

https://ec.europa.eu/docsroom/documents/37581/attachments/1/translations/en/renditions/native (last access 17/07/2022).

[21] A. RAVIZZA, E. CAIANI, E. SANTORO, S. STEFANELLI, F. STERNINI, *Come gestire gli aspetti regolatori per le terapie digitali*, in *Tendenze nuove*, Special Issue 1, 2021, 21, available at http://www.tendenzenuove.it/2021/01/13/come-valutare-le-terapie-digitali-da-un-punto-di-vista-clinico/ (access 17/07/2022).

[22] EU COMMISSION, *Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices*, Version 1.22, 22nd May 2019, https://ec.europa.eu/docsroom/documents/35582/attachments/1/translations/en/renditions/native (last access 17/07/2022).

[23] The borderline categories of software and mobile applications: *i)* mobile applications for processing ECGs; *ii)* mobile applications for the communication between patients and caregivers while giving birth; *iii)* mobile medical applications for viewing the anatomy of human bodies; *iv)* software for the interpretation of guidelines; *v)* software for the delivery and the management of cognitive remediations and rehabilitation programmes; *vi)* software for information management and the monitoring of patients; *vii)* mobile applications for the managing pictures of moles; *viii)* mobile applications for the assessment of moles; *ix)* devices intended to facilitate the conception based on basal body temperature; *x)* devices intended to facilitate the conception and enable the contraception based on basal body temperature; *xi)* stand-alone software application for conception and contraception purposes by means of data entered by the patient; and *xii)* medication decision support software.

[24] Article 2(30) MDR: "'manufacturer' means a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark".

[25] Article 2(32) MDR: "'authorised representative' means any natural or legal person established within the Union who has received and accepted a written mandate from a manufacturer, located outside the Union, to act on the manufacturer's behalf in relation to specified tasks with regard to the latter's obligations under this Regulation".

[26] Article 2(33) MDR: "'importer' means any natural or legal person established within the Union that places a device from a third country on the Union market".

[27] Article 2(34) MDR: "'distributor' means any natural or legal person in the supply chain, other than the manufacturer or the importer, that makes a device available on the market, up until the point of putting into service".

[28] Article 2(37) MDR: "'user' means any healthcare professional or lay person who uses a device".

[29] A. RAVIZZA, E. CAIANI, E. SANTORO, S. STEFANELLI, F. STERNINI, *op. cit.*, 27.

A) Safety. Particularly, with regards to Digital Therapeutics, to demonstrate the devices' safety, manufacturers may refer to: *a)* the IEC 62304:2006 standard,[30] that defines the lifecycle requirements for medical device software (so-called MDS), and whose purpose is to establish a common framework for their lifecycle processes; and *b)* the ISO 14971:2020 standard on the application of risk management to MDs. Pursuant to the former, the safety-class of the software depends on the gravity of the damage caused by the potential fault of the software itself. This determines the degree of scrupulousness that manufacturers shall perform. Although the version EN 62304 of IEC 62304 is considered as a harmonised rule, there is no correlation between the risk-classification set out in it (classes A to C) and in MDR (classes I to III). Hence, the manufacturer shall determine the risk-class of each device case by case.[31]

B) Clinical benefit.[32] The ISO 14155:2020 standard can be a reference, relating to good clinical practice for the design, conduct, recording and reporting of clinical investigations conducted in human subjects to assess the clinical performance/effectiveness and safety of MD. In the light of this standard, manufacturers shall demonstrate that, in the population-sample, the potential risk related to the application of the software is lesser that its clinical benefit. Moreover, as for the aspects not directly assessed in terms of specific clinical outcomes, one should mention the document MDCG 2020-1 *Guidance on Clinical Evaluation (MDR)/ Performance Evaluation (IVDR) of Medical Device Software*.[33]

C) Quality. One can refer to the ISO 13485:2016 standard about the quality management systems and requirements for regulatory purposes of MDs.

The obligations of the authorised representative are set out in Article 11.

The obligations of the importers are set out in Article 13 MDR, in the light of which they can place on the EU market only the devices that are in conformity with the Regulation.

The general obligations of distributors are set out in Article 14 MDR, pursuant to which, when making a device available on the market, they shall, in the context of their activities, act with due care in relation to the requirements applicable.

Article 16 MDR establishes the rules governing the cases in which the obligations of manufacturers apply to importers, distributors, or other persons.

4.3 The clinical evaluation and the clinical investigation

The relevant provisions concerning the issue of clinical evaluation and clinical investigations are set out in Chapter VI, Articles 61 to 82, and Annex XV MDR, whose scope includes "the requirements for clinical trials, study participants' consent, and the implementation with specific groups of patients,

[30] Note: this standard will soon be replaced by IEC/DIS 62304.3 (still under development on the 17th of July 2022).

[31] A. RAVIZZA, E. CAIANI, E. SANTORO, S. STEFANELLI, F. STERNINI, *op. cit.*, 28-29.

[32] Pursuant to Article 2(53) MDR, 'clinical benefit' "means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health".

[33] A. RAVIZZA, E. CAIANI, E. SANTORO, S. STEFANELLI, F. STERNINI, *op. cit.*, 29-31.

such as minors, pregnant women, emergency patients, breastfeeding, and other non-compliant patients".[34]

Pursuant to Article 61, manufacturers shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. Such evidence shall be appropriate in view of the characteristics of the device and its intended purpose. In this regard, they shall plan, conduct, and document a clinical evaluation.

Every clinical evaluation shall follow a defined and methodologically sound procedure. Also, the clinical evaluation and its documentation shall be updated throughout the lifecycle of the device concerned, and the clinical evaluation, its results and the clinical evidence derived from it shall be documented in a clinical evaluation report.

Article 62 sets the general requirements for clinical investigations, for the case they are carried out as part of the clinical evaluation for conformity assessment purposes, for one or more of the following purposes: first, to establish and verify that a device is designed, manufactured and packaged in such a way that it is suitable for one or more of the specific purposes mentioned above, and achieves the intended performance as specified by the manufacturer; second, to establish and verify the clinical benefits of a device as specified by the manufacturer; and third, to establish and verify the clinical safety of the device and to determine any undesirable side-effects and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device.

Two professional figures are fundamental, namely a sponsor on the one hand, taking responsibility for the initiation, the management and setting up of the financing of the clinical investigation, and the investigator on the other, *i.e.*, the individual responsible for the conduct of a clinical investigation at a clinical investigation site (see Article 2 (49) and (54) MDR).

According to Article 70, The sponsor shall apply to the Member State(s) in which the clinical investigation is to be conducted (so-called 'Member State concerned'). Within 10 days, the Member State concerned shall notify the sponsor as to whether the clinical investigation falls within the scope of MDR, and as to whether the application dossier is complete.

The conditions by virtue of which the sponsor may start the clinical investigation need to be mentioned. In a nutshell, while for investigational class I devices or non-invasive class IIa and class IIb devices, (unless otherwise stated by national law) the sponsor can initiate the investigation immediately after the application has been validated, inasmuch as a negative opinion has not been issued by an ethics committee in the Member State concerned; for all other investigational devices, the investigation can start as soon as the Member State concerned has notified the sponsor of its authorisation, and provided that a negative opinion has not been issued by an ethics committee in the Member State concerned.

The sponsor and the investigator shall ensure that an investigation is conducted in accordance with the approved clinical investigation plan (CIP), *i.e.*, a document setting out the rationale, objectives, design methodology, monitoring, conduct, record-keeping, and the method of analysis for the clinical investigation. They also shall record, process, handle, and store all clinical investigation information, in

[34] K. Becker, M. Lipprandt, R. Röhrig, T. Neumuth, *Digital health – Software as a medical device in focus of the medical device regulation (MDR)*, in *it - Information Technology*, 61, 5-6, 2019, 211-218, https://doi.org/10.1515/itit-2019-0026.

such a way that it can be accurately reported, interpreted, and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection (see the GDPR no. 679/2016).

In any case, the sponsor shall ensure adequate monitoring of the conduct of the clinical investigation (Article 72) and establish a procedure for emergency situations which enables the immediate identification and, where necessary, an immediate recall of the devices.

In case of modifications to the investigation that are likely to impact substantially on the safety, health, or rights of the subjects, or on the robustness or reliability of the clinical data generated by the investigation, the sponsor shall inform the Member State concerned (Article 75).

According to Article 80, the sponsor is responsible for the recording of: *a)* any adverse event of a type identified in the CIP as being critical to the evaluation of the results of that clinical investigation; *b)* any serious adverse event; *c)* any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; and *d)* any new findings in relation to any of these events. Furthermore, without delay, it shall report to all Member States concerned: *a)* any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible; *b)* any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; *c)* any new findings in relation to any of these events. Such duty to report concerns also the events occurred in third countries in which a clinical investigation is performed under the same CIP.

Three documents are crucial to clinical investigations, that is, the CIP, which has already been described above; the Investigator's Brochure (IB), containing all the clinical and non-clinical information on the investigational device that is relevant for the investigation, which shall constantly be updated; and finally, the Clinical Investigation Report (CIR), containing a critical evaluation of all the data collected during the clinical investigation, and include any negative findings.

Furthermore, three concepts need to be distinguished. Post-market surveillance (PMS), vigilance, and market surveillance.

While the PMS includes all activities carried out by manufacturers together with other economic operators, to institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they introduce into the economic circuit, for the purpose of identifying any need to immediately apply corrective or preventive actions; vigilance is only one of such activities and consists in a reactive system to manage incidents. Instead, the market surveillance refers to those activities performed by competent authorities to check and ensure that devices comply with the requirements set out in the relevant pieces of EU law.

In this regard, Article 83 specifies the obligations (enshrined in general in Article 10) of manufacturers concerning the PMS system. Depending on the risk-class of the devices, manufacturers shall prepare distinct types of reports.

This is crucial to the matter of AI-MDs. In fact, while for class I devices, manufacturers shall only prepare and update a report summarising the results and conclusions of the PMS (Article 85); for class IIa, class IIb and class III devices – which likely include all the AI-MDs – manufacturers shall similarly

prepare a report (the 'periodic safety update report' or 'PSUR') summarising the results and conclusions of the PMS, which however, unlike class I devices, shall be updated at least annually (Article 86).

5. The Legislation on Clinical Trials of Medicines for Human Use and Its Relevance To AI-MDs

The matter of clinical trials of medicines for human use is specifically governed by the so-called Clinical Trials Regulation 2014/536 (CTR),[35] which aims at harmonising the rules on clinical trials within the Union, and at simplifying the procedure of trials, so as to reduce the costs, to allow the transnational cooperation in international trials, to promote the competitiveness of the Union and the innovation, as well as to incentivise the development of new MDs.

The Regulation applies to all clinical trials conducted in the Union solely, not to non-interventional studies (Article 1 CTR), *i.e.*, clinical studies other than a clinical trial (Article 2.4 CTR). In this regard, Article 2 CTR defines differently the concepts of clinical study, and of clinical trial.

The former is "any investigation in relation to humans intended: (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; (b) to identify any adverse reactions to one or more medicinal products; or (c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products" (Article 2.2.1 CTR).

The latter is "a clinical study which fulfils any of the following conditions: (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects" (Article 2.2.2 CTR).

Also, CTR introduces the concept of low-intervention clinical trial, which "fulfils all of the following conditions: (a) the investigational medicinal products, excluding placebos, are authorised; (b) according to the protocol of the clinical trial, (i) the investigational medicinal products are used in accordance

[35] On the matter of clinical evaluation with regards to the EU legislation, see C. CASONATO, *I percorsi evolutive del diritto della sperimentazione umana: spunti per un'analisi comparata*, in C. BUCCELLI (ed.), *Aspetti etici della sperimentazione biomedica, Evoluzione, criticità, prospettive*, Napoli, 2015, 33-45; L. FIERRO, *L'UE verso la mondializzazione della sperimentazione clinica. Dalla semplificazione delle procedure ai diritti degli arruolati*, in *Rivista italiana di medicina legale (e del diritto in campo sanitario)*, 3, 2016, 971-995; C. PETRINI, S. GARATTINI, *Trials, Regulation and tribulation*, in *European Journal of Clinical Pharmacology*, 72, 4, 2016, 503-505, https://doi.org/10.1007/s00228-016-2009-1; M. FERRARI, *La nuova normativa per un approccio armonizzato alla regolamentazione delle sperimentazioni cliniche nei Paesi dell'UE*, in *Responsabilità civile e previdenza*, 2, 2016, 702-722; M. FASAN, *Il Regolamento UE n. 536/2014: la disciplina della sperimentazione clinica tra uniformità e differenziazione*, in *BioLaw Journal – Rivista di BioDiritto*, 2, 2017, 187-209, https://doi.org/10.15168/2284-4503-244; E. GEFENAS, A. CEKANAUSKAITE, J. LEKSTUTIENE, V. LUKASEVICIENE, *Application challenges of the new EU Clinical Trials Regulation*, in *European Journal of Clinical Pharmacology*, 73, 7, 2017, 795-798, https://doi.org/10.1007/s00228-017-2267-6; E. TENTI, G. SIMONETTI, M.T. BOCHICCHIO, G. MARTINELLI, *Main changes in European Clinical Trials Regulation (No 536/2014)*, in *Contemporary Clinical Trials Communications*, 11, 2018, 99-101, https://doi.org/10.1016/j.conctc.2018.05.014; L. FIERRO, *L'UE verso la mondializzazione della sperimentazione*, cit., 971; M.P. GENESIN, *La disciplina dei farmaci*, in S. RODOTÀ, P. ZATTI, R. FERRARA (ed.), *Trattato di biodiritto. Salute e sanità*, Milano, 2010, 619-623.

with the terms of the marketing authorisation; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned".

The main professional figures involved in clinical trials are the sponsor and the investigator.[36]

Each clinical trial may have one or more sponsors, who may delegate its tasks to an individual. Where the sponsor is not established in the EU, it shall have a legal representative therein. The latter shall be responsible for ensuring compliance with the sponsor's obligations and shall be the addressee for all the pertinent communications, which are deemed to be a communication to the sponsor (Article 74).

The figure of principal investigator – *i.e.*, the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site – shall "ensure compliance of a clinical trial at a clinical trial site with the requirements of this Regulation", and "shall assign tasks among the members of the team of investigators in a way which is not compromising the safety of subjects and the reliability and robustness of the data generated in the clinical trial at that clinical trial site" (Article 73).[37]

5.1 Does CTR apply to AI-MDs?

One should wonder whether CTR applies to AI-MDs. The solution is negative at least in part: in brief, it does not apply to MDs, except for the case of products that are a combination of medicines and AI-MDs. In this regard, the difference between medical devices and investigational medicinal products needs to be considered.[38]

The former has already been described.

The investigational medicinal product is defined as "a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial" (Article 2.2(5) CTR). Also, Article 1.2 of Directive 2001/83/EC (*concerning the Community code relating to medicinal products for human use*) defines a medicinal product as any substance/combination of substances which is presented for treating or preventing disease in human beings, or which may be administered to human beings in order to make a medical diagnosis or to restore, correct, or modify physiological functions in human beings.

[36] Pursuant to Article 71 CTR, the investigator and the sponsor may be the same person. One should note that, according to Article 75 CTR, such Regulation does not affect the civil and criminal liability of the sponsor, investigator, or persons to whom the sponsor has delegated tasks. However, Article 94 CTR requires Member States to lay down rules on effective, proportionate, and dissuasive penalties applicable to infringements of the Regulation and take all measures necessary to ensure that they are implemented.

[37] The investigator shall be medical doctors as defined in national law, or at least professionals recognised in the Member State concerned as qualified for being an investigator because of the necessary scientific knowledge and experience in patient care. Other individuals involved in conducting a clinical trial shall be suitably qualified by education, training, and experience to perform their tasks (Article 49 CTR).

[38] As for the conceptual and regulatory difference between MDs and medicinal products, see N. PARVIZI, K. WOODS, *Regulation of medicines and medical devices: contrasts and similarities*, in *Clinical Medicine*, 14, 1, 2014, 6-12, https://doi.org/10.7861/clinmedicine.14-1-6; M. RACCHI, S. GOVONI, A. LUCCHELLI, L. CAPONE, E. GIOVAGNONI, *Insights into the definition of terms in European medical device regulation*, in *Expert Review of Medical Devices*, 13, 10, 2016, 907-917, https://doi.org/10.1080/17434440.2016.1224644.

On this matter, it has been argued that the definitions overlap to some degree.[39] However, the main criterion to differentiate the cases is the definition and identification of the mechanism by which the product exerts its therapeutic effect: for medicinal products, the effect is achieved by a pharmacological, immunological, or metabolic mechanism of action; instead, MDs are any article intended by the manufacturer to be used, alone or in combination, for a specific medical purpose and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.[40]

Basically, two classes of articles can be distinguished.

On the one hand, medicinal products can include an AI-MD (so-called combination product), *i.e.*, some medicines are used in combination with an AI-MD, usually to enable the delivery of the medicine. There are two types of combination: *a)* integral, where the medicinal product and device form a single integrated product (*e.g.*, patches for transdermal drug delivery and pre-filled inhalers); and *b)* co-packaged, where the medicinal product and the device are separate items contained in the same pack (*e.g.*, an AI driven device for insulin injections). Especially the latter can be relevant in the case of digital health technologies, as they are integral part of the devices by which the medicine is delivered.

On the other hand, there are AI-MDs with an ancillary medicinal substance to support their proper functioning (*e.g.*, an AI-driven metered-dose inhaler).

Only the first class of articles falls under the legislation on medicines for human use, while the second one falls under the MDR. [41]

5.2 Clinical trials: the procedure

In order for a clinical trial to start, the sponsor shall submit an application dossier[42] to the Member States concerned and propose one of them as reporting Member State (Article 5).

The sponsor and the investigator comply with good clinical practice, as well as a protocol, *i.e.*, a document that describes the objectives, design, methodology, statistical considerations, and organisation of the clinical trial (Article 47).

The sponsor and/or the investigator, depending on the situation, shall comply with several obligations. The sponsor is responsible for the adequate monitoring of the conduct of a clinical trial, the extent and nature of which shall be determined on the basis of an assessment that takes into consideration all characteristics of the trial (Article 48). Also, it shall notify the Member States concerned about the serious breaches of CTR[43] (Article 52), all unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions, as well as all inspection

[39] Namely, they are both used in humans or are administered to humans for therapeutic or diagnostic purposes. Also, they may be substances or materials which are used in the treatment or prevention of diseases, or in the restoration of physiological functions presumed to be altered.

[40] M. RACCHI, S. GOVONI, A. LUCCHELLI, L. CAPONE, E. GIOVAGNONI, *op. cit.*, 909.

[41] See https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices#medicinal-products-that-include-a-medical-device-(%E2%80%98combination-products%E2%80%99)-section (last access 17/07/2022).

[42] Article 25 establishes that the application dossier for the authorisation of a trial shall contain all the relevant information and documentation specified in Annex I CTR.

[43] Namely, breaches likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

reports of third country authorities concerning the clinical trial (Article 53). If an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor, together with the investigator, is responsible for taking appropriate urgent safety measures, and shall notify the Member States concerned of such event and measures (Article 54).
The sponsor shall provide the investigator with the investigator's brochure (IB), which shall be updated where new and relevant safety information becomes available and reviewed at least once a year (Article 55).
The sponsor or investigator, as applicable, shall record, process, handle and store all clinical trial information, in such a way that it can be accurately reported, interpreted, and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection (Article 56).
Also, the sponsor, together with the investigator, shall keel a Clinical Trial Master File (CTMF), containing the documents about the clinical trial, which allow to verify the conduct of a clinical trial and the quality of the data generated (Article 57).[44] They shall keep the content of the CTMF for at least 25 years after the end of the clinical trial. Furthermore, the sponsor shall appoint, within its organisation, individuals responsible for archives. Only to such persons the access to archives shall be permitted (Article 58).

6. The European Medicines Agency (EMA) and the AI-MDs

It is common knowledge that the European Medicines Agency (hereinafter EMA) is an EU agency, governed by Regulation 726/2004/EC, whose mission is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health in the Union.[45] The main tasks of EMA are *a)* to assist the Member States and the EU Institutions providing for scientific and technical advice on the medicines' quality, safety, and efficacy; *b)* to draw up guidelines concerning the applications for marketing authorisation of medicines for human use; and *c)* to preside over the medicines' post-market surveillance and the pharmacovigilance.
The role of EMA is different depending on the distinction between combination products and AI-MDs with an ancillary medicinal substance.
In the first case, EMA is responsible for evaluating the quality, safety and efficacy of marketing authorisation applications, including the safety and performance of the AI-MD in relation to its use with the medicinal product.[46]

[44] The CTMF kept by the investigator and the one kept by the sponsor may have a different content, depending on the different nature of their responsibilities.
[45] See https://www.ema.europa.eu/en/about-us/what-we-do (last access 17/07/2022); R.F. KINGHAM, P.W.L. BOGAERT, P.S. EDDY, *The New European Medicines Agency*, in *Food and Drug Law Journal*, 49, 2, 1994, 301-21, http://www.jstor.org/stable/26659286; M. FILICE, *L'accountability della European Medicines Agency*, in *Rivista italiana di diritto pubblico comunitario*, 6, 2018, 1013-1052.
[46] On the 22nd of July 2021, EMA published a guideline (effective from the 1st of January 2022) describing the information that should be presented in the quality part of a marketing authorisation dossier for a medicinal product when it is used with a MD. Such guidance focuses on product-specific quality aspects of a MD (integral, co-packaged or separately-obtained and referenced in the product information), which may have an impact on the quality, safety and efficacy of a medicinal product. See EUROPEAN MEDICINES AGENCY (EMA) – COMMITTEE FOR

In the second case, EMA is responsible for an opinion, which shall be sought by the notified bodies before issuing a CE certificate, on the quality and safety of the ancillary substance. The Agency publishes consultation procedure public assessment reports (CPAR)[47] on its scientific opinions.[48]

EMA is also member of the International Coalition of Medicines Regulatory Authorities (ICMRA), that is a voluntary, executive-level, strategic coordinating, advocacy and leadership entity of regulatory authorities that cooperate to deal with emerging regulatory and safety challenges relating to medicines for human use, to coordinate their efforts in areas which are common to many authorities' mission, to identify areas for potential synergies and, where possible, leverage existing initiatives/enablers and resources.[49]

On the 6th of August 2021, ICMRA published a report containing recommendations to regulators to face the challenges linked to the use of AI in medicines.[50] Such report identifies key issues concerning the regulation of AI medicine and makes specific recommendations for regulators and stakeholders to foster the uptake of AI. Some of the main findings and recommendations include that regulators may need to apply a risk-based approach to assessing and regulating AI, which could be informed through exchange and collaboration in ICMRA; while sponsors, developers and pharmaceutical companies should establish strengthened governance structures to oversee algorithms and AI deployments that are closely linked to the benefit/risk of a medicinal product. Furthermore, pursuant to the report, regulatory guidelines for AI development,[51] validation and use with medicinal products[52] should be developed in areas such as data provenance, reliability, transparency and understandability, pharmacovigilance,[53] and real-world monitoring of patient functioning.[54]

MEDICINAL PRODUCTS FOR HUMAN USE (CHMP), *Guideline on quality documentation for medicinal products when used with a medical device*, the 22nd of July 2021, 19, https://www.ema.europa.eu/documents/scientific-guideline/guideline-quality-documentation-medicinal-products-when-used-medical-device-first-version_en.pdf (last access 17/07/2022).

[47] See https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices/ancillary-medicinal-substances-medical-devices/chmp-opinions-consultation-procedures.

[48] See https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices#medicinal-products-that-include-a-medical-device-(%E2%80%98combination-products%E2%80%99)-section, (last access June 2022)

[49] See http://www.icmra.info/drupal/en (last access 17/07/2022).

[50] INTERNATIONAL COALITION OF MEDICINES REGULATORY AUTHORITIES, *Horizon Scanning Assessment Report – Artificial Intelligence*, http://www.icmra.info/drupal/sites/default/files/2021-08/horizon_scanning_report_artificial_intelligence.pdf (last access 17/07/2022).

[51] See https://www.ema.europa.eu/en/glossary/guideline.

[52] See https://www.ema.europa.eu/en/glossary/medicinal-product.

[53] See https://www.ema.europa.eu/en/glossary/pharmacovigilance.

[54] See https://www.ema.europa.eu/en/news/artificial-intelligence-medicine-regulation (last access 17/07/2022).

7. The Commission's Proposal for an Artificial Intelligence Act (AIA)

On the 21st of April 2021, the EU Commission published a Proposal for a Regulation, addressed to the European Parliament and the Council, *'laying down harmonised rules on artificial intelligence (Artificial Intelligence Act) and amending certain Union legislative acts'*[55] (hereinafter 'the Proposal' or 'AIA').[56]

7.1 The Explanatory Memorandum and the Communication from the European Commission *'Fostering a European approach to Artificial Intelligence'*

The EU Commission specified the purpose of the Proposal by means of two different documents, *i.e.*, an *Explanatory Memorandum*, and a Communication, published on the same date by the EU Commission, entitled *'Fostering a European approach to Artificial Intelligence'* (hereinafter 'the Communication').[57]

The various documents on AI, adopted by the EU institutions over the last three years,[58] are summarised, and the draft AIA represents the culminating point of a three-year regulatory process.[59]

The 'twin objectives' of the Proposal are to address the issue of managing the risks associated with specific applications of AI on the one hand, and to promote the development of such technology on the other.[60]

In the Commission's opinion, only an approach based on the balance of values and the proportionality principle allows to achieve such goals, so that a normative package that is both future-proof and innovation-friendly is needed. In this regard, the Commission's intent is "to intervene only where this is

[55] COM (2021) 206 final.

[56] In fact, tons of amendments have already been submitted by each political group of the European Parliament. See https://www.euractiv.com/section/digital/news/ai-regulation-filled-with-thousands-of-amendments-in-the-european-parliament/ (last access 17/07/2022).

[57] COM (2021) 205 final.

[58] Namely, the *European AI Strategy* (April 2018), https://digital-strategy.ec.europa.eu/en/policies/european-approach-artificial-intelligence (last access 17/07/2022); the *Ethics guidelines for trustworthy AI* (April 2019), https://digital-strategy.ec.europa.eu/en/library/ethics-guidelines-trustworthy-ai (last access 17/07/2022), and the *Assessment List for Trustworthy Artificial Intelligence (ALTAI) for self-assessment* developed by the Commission's High Level Expert Group on AI (HLEG), https://digital-strategy.ec.europa.eu/en/library/assessment-list-trustworthy-artificial-intelligence-altai-self-assessment (last access 17/07/2022); the establishment of the AI Alliance, a platform designed to enable more than four thousand stakeholders to allow the debate on the technological and social implications of AI, https://digital-strategy.ec.europa.eu/en/policies/european-ai-alliance (last access 17/07/2022); a first *Coordinated Plan on AI*, published in December 2018, about which see recently https://digital-strategy.ec.europa.eu/en/library/coordinated-plan-artificial-intelligence-2021-review (last access 17/07/2022); the Commission's *White Paper on AI*, published in February 2020 (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0065&from=EN, last access 17/07/2022) together with a report on security and liability with regards to AI, Internet of Things (IoT) and robotics (https://ec.europa.eu/info/publications/commission-report-safety-and-liability-implications-ai-internet-things-and-robotics-0_en, last access 17/07/2022); and, finally, the public consultation on the aforementioned White Paper, that took place from February to June 2020, https://digital-strategy.ec.europa.eu/en/white-paper-artificial-intelligence-public-consultation-towards-european-approach-excellence-and (last access 17/07/2022).

[59] The Communication, cit., 5.

[60] The Communication, cit., 6.

strictly needed and in a way that minimises the burden for economic operators, with a light governance structure".[61]

The Proposal is based upon some elements which, considered together, identify a proportionate and risk-based European regulatory approach:[62] *a)* a technology-neutral definition of AI systems that is future-proof; *b)* the focus only on the so-called high-risk AI use cases, to avoid regulatory overreach;[63] *c)* the identification of certain specific requirements for high-risk AI systems; *d)* the ban on certain strictly identified uses of IA, justified by the high risk of infringement of EU values and fundamental rights; *e)* a restrictive approach with regards to remote biometric identification systems (*e.g.*, facial recognition tools);[64] *f)* minimal transparency requirements for AI uses other than the aforementioned ones;[65] and *g)* incentives for the use of regulatory sandboxes.[66]

In summary, the two-faced objective of the Proposal consists in the protection of fundamental rights, which is crucial for the realisation of a trustworthy AI, without inhibiting technological innovation, which, however, must be human-centric.[67]

As previously specified, the Proposal has been published together with an Explanatory Memorandum, which, in addition to the repetition of considerations contained in the Communication, serves as an introduction to the document describing the main elements.

The 'epistemological' premise of the legislative initiative at issue is that AI is likely to bring numerous benefits from a social and economic viewpoint. However, it is also likely to create new risks to the rights and values protected by EU law.[68] Hence, regulation is needed, to maximise the benefits and reduce the risks, and in particular: *a)* to ensure that the AI systems placed on (and used in) the EU single market are safe and applied in accordance with the fundamental rights and the EU values; *b)* to

[61] The Communication, cit., 6.

[62] The Communication, cit., 6-7.

[63] *Contra* P. GLAUNER, *An Assessment of the AI Regulation Proposed by the European Commission*, in S. EHSANI, P. GLAUNER, P. PLUGMANN, F.M. THIERINGER (ed.), *The Future Circle of Healthcare: AI, 3D Printing, Longevity, Ethics, and Uncertainty Mitigation*, Cham, 2022, 119-127.

[64] As a general rule, the real-time use of such systems for law enforcement purposes shall be prohibited in publicly accessible spaces, unless when exceptionally authorised by the law. However, they are subject to certain safeguards). In addition, all facial recognition systems shall undergo an *ex-ante* conformity assessment by a third-party certifying body and be subject to stricter requirements of logging and human control.

[65] The Communication, 7.

[66] See COUNCIL OF THE EUROPEAN UNION, *Council Conclusions on Regulatory sandboxes and experimentation clauses as tools for an innovation-friendly, future-proof and resilient regulatory framework that masters disruptive challenges in the digital age*, 13026/20, the 16th November 2020; as well as R. PARENTI, *Regulatory Sandboxes and Innovation Hubs for FinTech. Impact on innovation, financial stability and supervisory convergence – Study for the committee on Economic and Monetary Affairs, Policy Department for Economic, Scientific and Quality of Life Policies, European Parliament*, 24th September 2020, available at https://www.europarl.europa.eu/RegData/etudes/STUD/2020/652752/IPOL_STU(2020)652752_EN.pdf (last access 17/07/2022).

[67] The Communication, 1.

[68] In this regard, see *ex multis* C. CASONATO, *Potenzialità e sfide dell'intelligenza artificiale*, in *BioLaw Journal – Rivista di BioDiritto*, 1, 2019, 177-182, https://doi.org/10.15168/2284-4503-359; ID., *Costituzione e intelligenza artificiale: un'agenda per il prossimo futuro*, in *BioLaw Journal – Rivista di BioDiritto*, 2, 2019, 711-725, https://doi.org/10.15168/2284-4503-494; S. QUATTROCOLO, *Equo processo penale e sfide della società algoritmica*, in *BioLaw Journal – Rivista di BioDiritto*, 1, 2019, 135-144, https://doi.org/10.15168/2284-4503-356; S. RIONDATO, *Robot: talune implicazioni di diritto penale*, in P. MORO, C. SARRA (ed.), *Tecnodiritto: temi e problemi di informatica e robotica giuridica*, Milano, 2017, 85-98.

ensure legal certainty, so as to stimulate investment and innovation in the field of AI; *c)* to make more efficient the application of the rules already in force, in whose scope certain AI systems are likely to fall; and finally *d)* to create the conditions for the development of a single market for AI applications, based upon the values of legality, safety and trust.

The proposed set of harmonised rules concerns all the three phases of the AI systems' lifecycle, *i.e.*, the development, the marketing, and the concrete application.

The Proposal considers the relationship between the provisions of the AIA and the Union law in force, regulating key economic sectors in which high-risk AI systems are already applied (or are likely to be applied in a short time), *i.e.*, AI systems can constitute components of products whose development and application cycle is already governed by the EU law. Then, it will be necessary to ensure regulatory consistency, to avoid duplication and to minimise additional costs for economic operators.

With regards to products falling within the scope of the so-called New Legislative Framework (NLF) legislation, including MDs, the requirements for high-risk AI systems will be added to those already provided for by the relevant sectorial legislation. Hence, such integration will constitute the parameter for the comprehensive conformity assessment procedure. In view of this mutual regulatory interpenetration ("the interplay of requirements"),[69] while the Proposal refers to requirements aiming at a balanced management of the specific risks posed by AI systems, the rules of the NLF legislation guarantee the overall safety of the final product. In other words, the NLF legislation may include additional requirements, other than the ones referred to in the Proposal, related to the safe integration of an AI system within a wider class of products.[70]

Attention is paid to the matter of fundamental rights. The Commission is aware of introducing significant restrictions not only on the economic initiative freedom, but also on artistic and scientific freedom, which are protected by Articles 16 and 13 of the *EU Charter of fundamental rights*. However, such restrictions are considered necessary and justified to guarantee (prevailing) rights and freedoms which are fundamental too (*i.e.*, health, safety, and consumer protection).

7.2 The Proposal

Article 2 circumscribes the *ratione personae* scope of the Proposal: *a)* providers who place on the market or put into service[71] AI systems within the Union, regardless of whether they are based in the EU or in a third country; *b)* users[72] of IA systems located in the Union; and *c)* providers and users of systems which, although not developed/produced within the Union, generate output used in the EU. Moreover, the Regulation will not apply to systems developed or used exclusively for military purposes, or to the public authorities of a third State and international organisations, where these entities use AI

[69] See https://ec.europa.eu/growth/single-market/goods/new-legislative-framework_en (last access 17/07/2022).

[70] See also Recital 63 AIA.

[71] Article 3(2) AIA establishes that 'provider' "means a natural or legal person, public authority, agency or other body that develops an AI system or that has an AI system developed with a view to placing it on the market or putting it into service under its own name or trademark, whether for payment or free of charge".

[72] According to Article 3(4) AIA, 'user' "means any natural or legal person, public authority, agency or other body using an AI system under its authority, except where the AI system is used in the course of a personal non-professional activity".

systems in the framework of international agreements for law enforcement and judicial cooperation purposes.[73]

Since there is no unique notion of AI, the effort of the Commission in trying to define it is particularly appreciable from the point of view of legal certainty.[74]

The concept of AI is built around the fundamental (functional) characteristics of the software, considering, among other things: *a)* the variable levels of autonomy of the systems, on the one hand, and the possibility that they are used either as stand-alone devices or as components of more complex products, regardless of their physical integration into them (*i.e.*, both embedded and non-embedded systems), on the other. Article 3(1) states that an artificial intelligence system (or AI system) "means software that is developed with one or more of the techniques and approaches listed in Annex I[75] and can, for a given set of human-defined objectives, generate outputs such as content, predictions, recommendations, or decisions influencing the environments they interact with".

As already mentioned, AI can both create opportunities for society[76] and threat fundamental legal interests, primarily life, health, and safety of individuals.[77] Hence, in the light of a risk-based approach, the Proposal does not provide for a ban (which essentially would be based upon the precautionary principle)[78] on certain practices considered so risky that they cannot be admitted in any way. Instead,

[73] According to Article 3(41) AIA, 'law enforcement' "means activities carried out by law enforcement authorities for the prevention, investigation, detection or prosecution of criminal offences or the execution of criminal penalties, including the safeguarding against and the prevention of threats to public security".

[74] *Contra* M. EBERS, V.R.S. HOCH, F. ROSENKRANZ, H. RUSCHEMEIER, B. STEINRÖTTER, *The European Commission's Proposal for an Artificial Intelligence Act—A Critical Assessment by Members of the Robotics and AI Law Society (RAILS)*, in *J – Multidisciplinary Scientific Journal*, 4, 4, 2021, 589-603, https://doi.org/10.3390/j4040043; see also D. BOMHARD, M. MERKLE, *Europäische KI-Verordnung*, in *Der aktuelle Kommissionsentwurf und praktische Auswirkungen. Recht Digit*, 6, 2021, 276-283.

[75] Annex I AIA: "(a) Machine learning approaches, including supervised, unsupervised and reinforcement learning, using a wide variety of methods including deep learning; (b) Logic- and knowledge-based approaches, including knowledge representation, inductive (logic) programming, knowledge bases, inference and deductive engines, (symbolic) reasoning and expert systems; (c) Statistical approaches, Bayesian estimation, search and optimization methods".

[76] Recital 3 AIA.

[77] Recital 4 AIA.

[78] N.M. DE SADELEER, *The Precautionary Principle in EU Law*, in *Aansprakelijkheid Verzekering En Schade*, 5, 2010, 173-184, available at https://ssrn.com/abstract=2293606 (last access 17/07/2022); ID., *The Precautionary Principle in EC Health and Environmental Law*, in *European Law Journal*, 12, 2 2006, 139-172, https://doi.org/10.1111/j.1468-0386.2006.00313.x; K.R. FOSTER, P. VECCHIA, M.H. REPACHOLI, *Science and the Precautionary Principle*, in *Science*, 288, 5468, 2000, 979-981, https://doi.org/10.1126/science.288.5468.979; P. JIANG, *A Uniform Precautionary Principle under EU Law*, in *Peking University Transnational Law Review*, 2, 2, 2014, 490-518, available at https://ssrn.com/abstract=3058642 (last access 17/07/2022); R. VON SCHOMBERG, *The Precautionary Principle: Its Use Within Hard and Soft Law*, in *European Journal of Risk Regulation*, 3, 2, 2012, 147-156, https://doi.org/10.1017/S1867299X00001987; J. TOSUN, *HOW THE EU HANDLES UNCERTAIN RISKS: UNDERSTANDING THE ROLE OF THE PRECAUTIONARY PRINCIPLE*, in *Journal of European Public Policy*, 20, 10, 2013, 1517-1528, https://doi.org/10.1080/13501763.2013.834549; I. GOLDNER LANG, *"Laws of Fear" in the EU: The Precautionary Principle and Public Health Restrictions to Free Movement of Persons in the Time of COVID-19*, in *European Journal of Risk Regulation*, 2021, 1-24, https://doi.org/10.1017/err.2020.120; S.O. HANSSON, *How Extreme Is the Precautionary Principle?*, in *NanoEthics*, 14, 3, 2020, 245-257, https://doi.org/10.1007/s11569-020-00373-5; G.C. LEONELLI, *Judicial Review of Compliance with the Precautionary Principle from Paraquat to Blaise : "Quantitative*

the 'core' of AIA is identified both in the requirements that high-risk systems shall satisfy, and in the corresponding obligations for the economic operators involved in their lifecycle. Finally, according to the proportionate principle, less stringent transparency requirements are introduced with regards to specific non-high-risk systems.[79]

According to Article 6, two classes of high-risk systems can be identified.

In the first place, where the system is one of those listed in Annex III, it shall be considered high-risk.

In the second place, another criterion for a system to qualify as high-risk consists in the satisfaction of at least one of the following conditions: *a)* it is intended to be used as a safety component[80] of (or is itself) a product falling within the scope of the harmonised legislation referred to in the acts listed in Annex II, including the MDR EU/2017/745 on medical devices; *b)* the product of which it is a safety component (or the AI system as a standalone product), where required by the aforementioned harmonised legislation, shall be subject to the conformity assessment of a third-party certifying body, before being placed on the market or put into service.

Hence, most likely, AI-MDs always qualify as high-risk systems under the draft AI Act.

Article 8 makes clear that the requirements for high-risk systems are mandatory. They can be summarised as follows. The datasets used for the training and validation of the systems shall meet high quality parameters (see Article 10), so that their performance is safe and in line with the intended use.[81] Before a system is put into the economic circuit, the relative technical documentation shall be prepared, and shall demonstrate compliance with the requirements of the AIA (Article 11).[82] Systems shall be programmed and developed in such a way to allow, at the time of their use, the automatic recording of events (so-called "logs"), thus ensuring the traceability of their usage throughout the whole lifecycle and, therefore, the monitoring of operations for post-market surveillance purposes (Article 12). Pursuant to Article 13, the algorithms shall be transparent, so as to allow users to interpret the output. In addition, each system shall be accompanied by a series of concise, complete, correct, and clear instructions for use concerning: the provider and/or his representative, and the characteristics, capabilities and limitations of the system; the expected changes – which shall be pre-determined – in the system and its operation; human control measures, including the ones regarding the interpretation of outputs; an estimation of the systems duration, as well as any maintenance and care measures, including updates.[83]

Human control of systems is crucial to prevent or minimise the risks to health, safety, or other fundamental rights, in relation both to the intended use and to the foreseeable improper use of the device. For this purpose, AIs shall be programmed and developed in such a way to ensure (Article 14).[84]

Thresholds," Risk Assessment, and the Gap Between Regulation and Regulatory Implementation, in *German Law Journal*, 22, 2, 2021, 184-215, https://doi.org/10.1017/glj.2021.3.

[79] Recital 14 AIA.

[80] According to Article 3(14) AIA, 'safety component of a product or system' "means a component of a product or of a system which fulfils a safety function for that product or system or the failure or malfunctioning of which endangers the health and safety of persons or property".

[81] See *amplius* Recitals 44 and 45 AIA.

[82] See also Recital 46 AIA.

[83] See also Recital 47 AIA.

[84] See also Recital 48 AIA.

The systems must guarantee an appropriate level of precision and robustness, and with specific reference to the so-called dynamic systems (that is, those which continue to learn after their development and commercialisation), the possibility to intervene on any output affected by bias through timely corrective measures shall be ensured. Also, concerning the matter of cybersecurity, the system shall be resilient to attempts by unauthorised third parties to alter their use or their performance, for instance manipulations of training datasets, or the intentional preparation of fallacious inputs to cause an error (Article 15).[85]

Articles 16 to 29 identify the subjects responsible for the observance of the aforementioned requirements,[86] *i.e.*, the provider (Articles 16 to 23); the producers (Article 24); the authorised representatives of providers not established in the Union, where it is not possible to identify an importer (Article 25); the importers of systems developed outside the EU (Article 26); the distributors (Article 27); and the users (Article 29).

In a nutshell, pursuant to Article 16,[87] the provider shall: *a)* ensure compliance with the requirements of high-risk systems set out in Articles 8 to 14; *b)* equip themselves with a system for managing the quality of the systems (see *amplius* Article 17); *c)* prepare the technical documentation of such systems; *d)* ensure that the conformity assessment procedure has been passed, before systems are put in the economic circuit; *e)* record stand-alone systems in a database (managed provided for in Article 51); and, finally, *f)* have an adequate system for the post-market surveillance.

Where a high-risk AI system constitutes the safety component of a product falling within the scope of a NLF Act (*e.g.*, MDR) and is not marketed independently of that product, the manufacturer of such product shall be responsible for the compatibility of the system with the rules set out in the AIA (Article 24 and Recital No. 55).

[85] See also Recitals 49 to 51 AIA.

[86] These provisions define the scope of certain powers and duties corresponding to given roles. They aim at protecting certain fundamental legal interests. Particularly, obligations are specified with regards both to their content and to the subjects bound to their respect. Hence, they are 'legal duties to act' (instead of general diligence rules), whose violation can establish commission-by-omission criminal responsibility. From a comparative law point of view, one might recall: the so-called '*posizioni di garanzia*' in the Italian legal system, see F. SGUBBI, *Responsabilità penale per omesso impedimento dell'evento*, Padova, 1975; G. FIANDACA, *Il reato commissivo mediante omissione*, Milano, 1979; G. GRASSO, *Il reato omissivo improprio. La struttura obiettiva della fattispecie*, Milano, 1983; L. BISORI, *L'omesso impedimento del reato altrui nella dottrina e nella giurisprudenza italiane*, in *Rivista italiana di diritto e procedura penale*, 4, 1997, 1339-1394; M. ROMANO, *Commentario sistematico del codice penale*, Milano, 2004, 375-396; the so-called '*Garantenstellungen*' in the German legal system, see H.H. JESCHECK, T. WEIGEND, *Lehrbuch des Strafrecht. Allgemeiner Teil*, Berlin, 1996, 598-640; ARMIN KAUFMANN, *Die Dogmatik der Unterlassungsdelikte*, Göttingen, 1959; H.J. RUDOPLHI, *Die Gleichstellungsproblematik der unechten Unterlassungsdelikte und der Gedanke der Ingerenz*, Göttingen, 1966; R.D. HERZBERG, *Die Unterlassung im Strafrecht und das Garantenprinzip*, Berlin/New York, 1972; G. FREUND, *Erfolgsdelikt und Unterlassen: zu den Legitimationsbedingungen von Schuldspruch und Strafe*, Köln, 1992; J. VOGEL, *Norm und Pflicht bei den unechten Unterlassungsdelikten*, Berlin, 1993; A. GRÜNEWALD, *Zivilrechtlich begründete Garantenpflichten im Strafrecht?*, Berlin, 2001; and the so-called 'legal duties to act' in common law systems, see G.P. FLETCHER, *Rethinking criminal law*, Oxford/New York, 2000, 420-426 and 585-634; P.H. ROBINSON, *Structure and Function in Criminal Law*, Oxford, 1997, 16-56; J. HERRING, *Criminal Law: Text, Cases, and Materials*, New York, 2012, 110-117.

[87] See also Recital 54 AIA.

Where the AI system is developed outside the EU and an importer is not identifiable, third-country providers shall, by written delegation, identify an authorised representative in the EU (Article 25 and Recital No 56).
There are also some specific obligations for importers and distributors (Articles 26 and 27, and Recital No. 57).
Users shall use the systems in accordance with the instructions for use and monitor them accordingly. Also, in so far input data can be monitored, they shall ensure the consistency of such data with the intended purpose of the system. Moreover, they shall conduct an impact-assessment regarding the protection of personal data, according to Article 35 EU/2016/679 Regulation, and Article 27 EU/2016/680 Directive.

8. Conclusive remarks

We can try to clearly answer the two questions addressed in this article, that is, whether digital health, digital medicine and digital therapeutics are medical devices in the light of EU law; and, subordinately, what are the requirements that shall be respected by the various economic actors involved in such devices' lifecycle (notwithstanding how they are named in each piece of EU legislation).
About the first question, from all the aforementioned one can conclude that such technologies are medical devices in the light of the definition thereof provided for in the MDR. However, this conclusion needs to be clarified as follows: where a pharmaceutical product is integrated into the AI-device, the law applicable depends on the fact that such a medicine is ancillary, in which case MDR applies, or non-ancillary, in which case the legislation on medicines for human use applies.
In addition, it should be noted that the applicability of the draft AIA to the devices in question will basically depend on the definition of AI that will be finally adopted. In this regard, some scholars criticised the definition proposed by the European Commission, maintaining that it is "overly broad" and "covers almost every computer program".[88] On this matter, an interesting opinion has been expressed in a recent report issued by the Centre for European Policy Studies (CEPS): while [a] broad definition might entail that the legislation affects most software or algorithms circulating in the EU single market, even if the risk-based approach adopted by the AI Act and the introduction of Annex I potentially mitigate the risk"; "[o]n the other hand, adopting a narrow definition may imply that the regulatory requirements […] only apply to a subset of AI systems". According to such report, a solution might be to refer either to the definition of (trustworthy) AI already developed by the Commission's High-Level Group of Experts on AI (AI HLEG),[89] or to the internationally agreed one by the Organisation for Economic Cooperation and Development (OECD) "as advocated by the opinion[90] of the Committee on

[88] M. EBERS, V.R.S. HOCH, F. ROSENKRANZ, H. RUSCHEMEIER, B. STEINRÖTTER, *op. cit.*, 590.
[89] See https://digital-strategy.ec.europa.eu/en/policies/expert-group-ai (last access 27/09/2022).
[90] EUROPEAN PARLIAMENT – COMMITTEE ON INDUSTRY, RESEARCH AND ENERGY, *Opinion on the 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*, COM(2021)0206 – C9-0146/2021 – 2021/0106(COD), available at https://www.europarl.europa.eu/doceo/document/ITRE-AD-719801_EN.pdf (last access 27/09/2022).

Industry, Research and Energy (ITRE) in the EP".[91] However, while the former focuses on how AI systems should be (*i.e.*, lawful, ethical, and robust), rather than clearly state what AI systems are; the latter is clearer to the point: "[a]n AI system is a machine-based system that can, for a given set of human-defined objectives, make predictions, recommendations, or decisions influencing real or virtual environments. AI systems are designed to operate with varying levels of autonomy".[92]
It is self-evident that the OECD's Recommendation cuts model-based systems out of the definition of AI. Yet, on closer inspection, whether this conclusion is appreciable from a *de lege ferenda* viewpoint is, at least, debatable.
As for the second question investigated in this article, the provisions of the relevant pieces of EU legislation described above (*i.e.*, MDR, legislation on clinical trials of medicines for human use and AIA) can be coordinated, to identify the rules applicable to AI-based MDs overall (a '*reductio ad unum*'). Such rules can be classified by way of subjective criterion, *i.e.*, with reference to the various subjects involved in the lifecycle of AI-based MDs.

– It is useful to examine the obligations of manufacturers together with the ones of providers. According to Article 2(30) MDR, manufacturer is any "natural or legal person who manufactures or fully refurbishes [i.e., renovates] a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark"; while according to Article 3(2) AIA, the provider is any "natural or legal person, public authority, agency or other body that develops an AI system or that has an AI system developed with a view to placing it on the market or putting it into service under its own name or trademark […]".
Particularly, two elements should be pointed out: first, in case of AI-MDs, the verbs "to manufacture" on the one hand, and "to develop" on the other, do have an analogous semantic scope; second, such manufacturing (or refurbishment) and development are carried out by the manufacturer/provider with the intent to put the product in the economic circuit "under its own name or trademark". In short, the manufacturer and the provider can sometimes coincide since the definitions set out in the MDR and in the draft AIA overlap somehow.
Misunderstandings must be avoided. For this reason, the term "developer", instead of "provider", is preferrable[93] and will hereinafter be used to indicate the subjects who develops AI-MDs.
Developers are always bound not only to the obligations set out in Article 10 MDR (entitled *General obligations of manufacturers*), but also to those enshrined in Article 16 AIA. Also, since the MDR is a so-called New Legislative Framework act, where a high-risk AI system constitutes

[91] A. Bogucki, A. Engler, C. Perarnaud, A. Renda, *CEPS IN-DEPTH ANALYSIS – THE AI ACT AND EMERGING EU DIGITAL ACQUIS: Overlaps, gaps and inconsistencies*, 02/09/2022, available at https://www.ceps.eu/ceps-publications/the-ai-act-and-emerging-eu-digital-acquis/ (last access 27/09/2022), 19.
[92] OECD, *Recommendation of the Council on Artificial Intelligence*, OECD/LEGAL/0449, available at https://legalinstruments.oecd.org/en/instruments/OECD-LEGAL-0449 (last access 27/09/2022), 7.
[93] Some amendments have been submitted in the European Parliament in this sense: see https://www.europarl.europa.eu/committees/en/imco/documents/latest-documents (access 27/09/2022); A. Bogucki, A. Engler, C. Perarnaud, A. Renda, *CEPS IN-DEPTH ANALYSIS – THE AI ACT AND EMERGING EU DIGITAL ACQUIS*, *op. cit.*, 20.

the safety component of a MD and is not marketed independently of such product, they shall be responsible for the compatibility of the system with the rules of the AI Act.

– The joint reading of Article 2(33) MDR and Article 3(6) AIA allows to define the importer as any natural or legal person established within the EU that places on the market or puts into service an AI-based MD that bears the name or trademark of a natural or legal person established outside the Union. The obligations binding the AI-MDs importers are set out both in Article 13 MDR and in Article 26 AIA.
– AI-MDs' distributors are any natural or legal person in the supply chain, other than the developer or the importer, which makes an AI-based MD available on the EU market without affecting its properties.[94] Pursuant to Article 14 MDR and Article 27 AIA, before making a high-risk AI-based MD available on the market or putting it into service, distributors shall act with due care in relation to the applicable requirements. They shall ensure that, while the device is under their responsibility, storage or transport conditions comply with the conditions set by the developer, and where receiving complaints or reports from healthcare professionals, patients or users about suspected incidents related to a device, they shall immediately forward this information to the developer and, where applicable, its authorised representative, and the importer.[95] Also, where the distributors consider or have reason to believe that the device presents a serious risk or is a falsified device, they shall inform the competent authority of the Member State in which they are established.
– As already mentioned, medicinal products may include an MD (so-called combination products), as well as MDs may incorporate, as an integral part, a substance which, if used separately, would be considered a medicinal product. In the latter case, a question of understanding the law applicable arises, namely either the MDR, or the CTR.

  Concerning such issue, it can be maintained that pursuant to Article 1 MDR, where the medicinal product incorporated into the MD does have an action ancillary to such device, this shall be assessed and authorised in accordance with MDR. Instead, when it does have an action that is principal (*i.e.*, non-ancillary), the integral product shall be governed by Directive 2001/83/EC on the Community code relating to medicinal products for human use, or Regulation 726/2004/EC on the Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and the establishment of EMA, as applicable. These two pieces of legislation are recalled by CTR. However, in such case, the relevant general safety and performance requirements set out in Annex I MDR shall apply as far as the safety and performance of the device part are concerned.

  Thus, the provisions of both MDR and CTR apply.

  In this regard, the rules on two important subjects involved in the lifecycle (particularly, the pre-market phase) of the products in question are of foremost importance: namely, the

[94] See Article 2(34) MDR and Article 3(7) AIA.

[95] For this purpose, they shall keep a register of complaints, of non-conforming devices and of recalls and withdrawals. Upon request by a competent authority, they also shall provide it with all the available information and documentation to demonstrate the conformity of a device.

sponsors and the investigators. The law applicable to them can be read by considering both MDR and CTR.

One should remind the conceptual difference between clinical studies (or investigations) on the one hand, and clinical trials on the other. Such difference has already been described. It is relationship between *genus* and *species*: *i.e.*, clinical trial is a *species* of the *genus* clinical investigation, consisting in the clinical study that satisfies the conditions enlisted in Article 2.2(2) CTR.

Where both MDR and CTR apply to the pre-market phase, it is useful to refer both to clinical studies and to clinical trials, to obtain an overview of what being a sponsor/investigator means, and which obligations such subjects are bound to. Concisely, the sponsor of a clinical study/trial is any individual, company, institution, or organisation which takes responsibility for the initiation, for the management and setting up of the financing of such investigation/trial;[96] while the investigator of a clinical study/trial is any individual responsible for the conduct of such study/trial at a clinical investigation/trial site.[97]

Pursuant to MDR, the sponsor (alone, together with, or alternatively to the investigator, as appropriate) shall comply with several obligations concerning the conduct of clinical investigations.

– Where the developer and the sponsor are not established in the EU, they shall appoint an authorised representative.[98] The overall regulation arises from the reading of both MDR and AIA. Pursuant to Article 11 MDR, they shall perform the tasks specified in their mandate. Also, according to Article 25 AIA, the mandate shall empower the authorised representative to carry out the following tasks: *a)* to keep a copy of the EU declaration of conformity and the technical documentation at the disposal of the national competent authorities with regards to the market surveillance; *b)* to provide a national competent authority (upon request) with all the information and documentation necessary to demonstrate the conformity of a high-risk AI system; and *c)* to cooperate with a national competent authority (upon request) on any action to be taken with respect to the AI system.
– Finally, users can be defined as any healthcare professional or lay person, legal person, public authority, agency, or other body using an AI-MD under its authority.[99] Apart from the obligations of users-healthcare professionals, namely the specific rules of conduct specified in medical guidelines and best practices (where existing and applicable) or the general duty of care they shall comply with when they practise, and without prejudice to other obligations under EU or national law, Article 29 AIA establishes a series of obligations for high-risk AI systems' users:
    a) to use such systems in accordance with the instructions of use accompanying them;

[96] See Article 2(49) MDR and Article 2.2(14) CTR.
[97] See Article 2(54) MDR and Article 2.2(15) CTR.
[98] Namely, a natural or legal person established within the Union who has received and accepted a written mandate to perform and conduct on their behalf the obligations they are bound to (see Article 2(32) MDR, Article 74 CTR, and Article 3(5) AIA).
[99] See Article 2(37) MDR and Article 3(4) AIA.

b) to ensure that input data is relevant in view of the intended purpose of the system, to the extent they exercise control over such data;
c) to monitor the operation of the system following the instructions of use;
d) to inform the developer or the distributor and suspend the use of the AI-MD if they have reasons to consider that its application in accordance with the instructions of use may result in a risk;
e) similarly, to inform the aforementioned subjects when they have identified any serious incident or any malfunctioning (and, of course, to interrupt the device's use);
f) to keep the logs automatically generated by the system, to the extent such logs are under their control; and finally
g) to use the relevant information they received to comply with their obligation to carry out a data protection impact-assessment under Article 35 of Regulation (EU) 2016/679 or Article 27 of Directive (EU) 2016/680, where applicable.