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Good Machine Learning Practices, Impact and Exploitation

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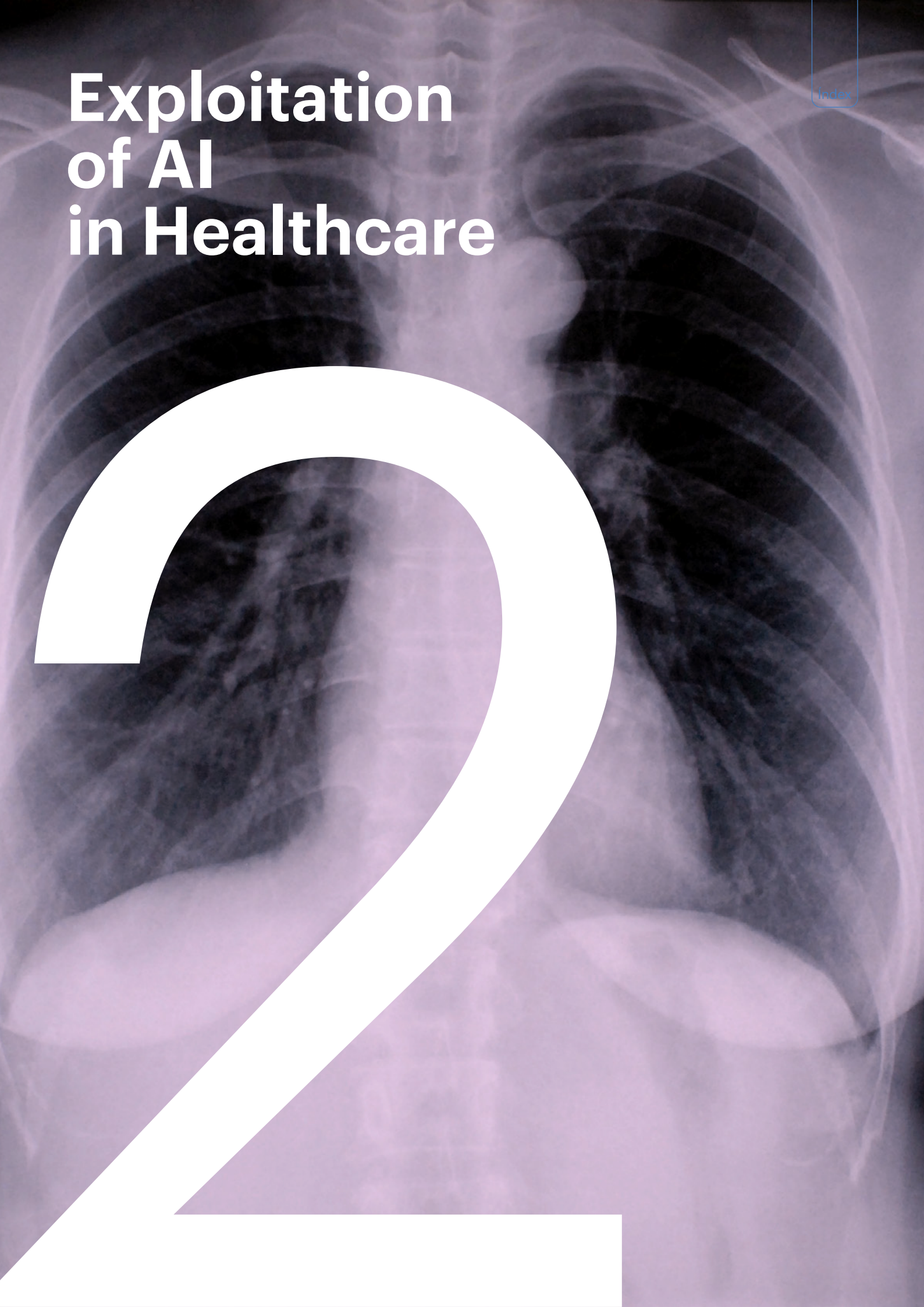
Introduction

Algorithms now underpin an increasing number of important decisions about individuals' lives in general and healthcare as is the case for the different use-cases of PAI. This raises serious ethical and legal concerns for the EU's future use of AI in its member states. In this regard, IP protection of assets for guaranteeing exploitation rights of AI-based healthcare products, health technology assessment, which summarize information about medical, economic, social, and ethical issues related to the use of health technologies are extremely important. AI-based products not being an exception to this rule. Moreover, medical equipment for diagnostic, treatment and prevention based on machine learning techniques are also subject to the medical device directives such as the ISO13485 and, as such, must follow a regulatory compliance process before they are launched. This short document presents an overview of the exploitation of AI in healthcare with a special emphasis in IP protection, Health Technology Assessment, Regulatory Issues and Business Models.

Exploitation of AI in Healthcare



2

IP protection

The acquisition/preparation of training data, the design of an appropriate model architecture (e.g., choosing suitable AI algorithms, setting initial parameter values), model training, evaluation, and optimization are all part of the general workflow of building an AI model solution for a defined problem. Furthermore, big, high-quality, representative training datasets are critical for an AI model's consistent performance while processing fresh data. Thus, business value is found in protecting. (i) AI models and/or algorithms, (ii) software in which the models/algorithms are contained, (iii) training, validation and/or optimization procedures, (iv) training data, (v) outcome data (i.e. end-product). IP protection may be sought for all or part of these prospective assets.

Copyright also provides different options for protecting AI, such as source code, database structures, data collections, and data models to be used for AI.

The European Patent Convention (EPC) states that mathematical models and algorithms are not patentable. However, AI inventions are generally patentable as a subgroup of computer-implemented inventions (CIIs). Also, according to the EPC, only those aspects that contribute to the technical nature of an invention can be used to measure originality [1]. Non-technical features (such as algorithms) that interact with technical features to solve a certain technical problem must be considered too. Protectable subject matter differs from country to country depending on what is addressed (e.g. product vs. method) and technical field.

Utility models, sometimes known as Utility Certificates, can protect technological ideas in several nations [2]. Protectable subject matter varies by nation and technological discipline, as well as the sort of subject matter (product vs. method). In most nations, the standards for obtaining a utility model are less strict. Because most nations lack substantive examination, the registration and publication procedure are easier, quicker, and less expensive. Utility models should be regarded as a rapid and low-cost solution to get IP protection for AI ideas that are frequently "immediately" obsolete.
In Germany, for example, it is possible to "branch-off" a utility model from an earlier patent application while keeping the patent application's priority and filing date. In a few weeks, the "branch-off" utility model might be registered. This strategy may be considered to obtain an enforceable IP right while the patent application is examined.

Finally, the Directive EU 2016/943 [3] has harmonized trade secret protection across the EU. An owner is entitled to protection against unlawful acquisition and use of a trade secret and is entitled to damage claims in case of misappropriation. Trade secrets may provide the broadest scope of IP protection. However, to rely on it, the directive requires an owner to implement internal trade secret policies and protocols to protect their know-how. Relevant technical information must be documented to prove possession of the know-how in case of litigation.

Health Technology Assessment (HTA)

Health Technology Assessment (HTA) consists of the systematic evaluation of properties, effects and/or impacts of health-care technology. It normally includes medical, social ethical and economic dimensions with the main objective of informing decision-making in healthcare.
A typical HTA assesses the benefits, efficacy, clinical and technical safety, and issues surrounding coverage and reimbursement, pricing decisions, clinical guidelines and protocols, and lastly, medical device regulation. HTA improves the uptake of cost-effective new technologies and prevent the uptake of technologies that are of doubtful value for the health system.
HTA is used to define which benefits to include while carrying out evidence-based assessments. New technologies are usually costlier than older ones and contribute to rising health expenditures. In this context the HTA process ensures that a new technology is not added until it is proven to be effective. Meanwhile, an older technology is not removed from the health package until it is shown to be ineffective or not cost-effective. HTA is also concerned with quality and the role of new technologies to improve health outcomes.

Regulatory and CE mark

AI-based systems for diagnosis, are considered medical devices under regulation 745/2017, which is mandatory for healthcare manufacturers. The manufacturer of these products must ensure compliance and, to do so, must perform the following steps:

Quality management system

MDR Regulation, chapter II article 10.9:
Manufacturers shall ensure that procedures are in place so that production in
series maintains conformity with the provisions of this Regulation. (...) The quality management system shall cover all parts and elements of the manufacturer's organization concerned with the quality of processes, procedures, and products. It will regulate the structure, responsibilities, procedures, processes, and resources management required to put into practice the principles and actions necessary to achieve compliance with the provisions of this Regulation. management system of quality will address, as a minimum, the following aspects:

1. A strategy for regulatory compliance, including compliance with conformity assessment procedures and management procedures for modifications of the products included in the system.
2. Determining applicable general safety and performance requirements and exploring options to achieve them.
3. Management responsibility.
4. Resource management, selection and control of suppliers and subcontractors.
5. Risk management.
6. Clinical evaluation in accordance with Article 61 and Annex XIV, including post-marketing clinical follow-up.
7. The realization of the products, including planning, design, development, production, and provision of services.
8. Verification of unique product identification number assignments made in accordance with Article 27(3) to all relevant products by ensuring the consistency and validity of the information provided in accordance with Article 29.
9. The establishment, application, and maintenance of a post-market monitoring system in accordance with Article 83.
10. The communication with the competent authorities, notified bodies, other economic operators, customers, and other interested parties.
11. The processes of notification of serious incidents and security corrective actions in the context of surveillance.
12. The management of corrective and preventive actions and the verification of their effectiveness.
13. The processes of monitoring and measuring production, data analysis and product improvement.

Technical Documentation

MDR Regulation, chapter II article 10.4:
Manufacturers of products other than custom products will develop and update technical documentation for such products. The technical documentation will allow the conformity of the product to be assessed with the requirements of this regulation. The technical documentation will contain the elements specified in annexes II and III. The Commission shall be empowered to adopt delegated acts in accordance with Article 115 which, in the light of technical progress, amend Annexes II and III.

To guarantee compliance, the manufacturer must produce the following documents:

- Plan, analysis and management of risks and benefits
- Cybersecurity
- User manual
- Labeling of the application and accessories
- Usability and performance tests
- Summary of technical documentation (including UDI code, EMDN, classification etc)
- Software development and validation plan
- Principles of operation
- State of the Art.

Clinical Documentation

MDR Regulation, chapter VI article 61:
(...) The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate compliance with the corresponding general safety and performance requirements. This level of clinical testing will be appropriate taking into account the characteristics of the product and its intended purpose.
To this end, manufacturers shall plan, carry out and document a clinical evaluation in accordance with this Article and Part A of Annex XIV.
(...) 3. The clinical evaluation will follow a defined and methodologically founded procedure based on the following:

1. a critical appraisal of the then-available relevant scientific literature on the product's safety, performance, design features, and intended purpose, when the following conditions are met:
    - it is demonstrated that the device subject to clinical evaluation with respect to the intended purpose is equivalent to the device to which the data refer, in accordance with section 3 of Annex XIV, and

- the data adequately demonstrates compliance with the relevant general safety and performance requirements.

2. a critical appraisal of the results of all available clinical investigations with due regard to whether the investigations were conducted under Articles 62 to 80, any act adopted under Article 81 and Annex XV, and
3. a consideration of alternative treatment options currently available for the same purpose, if any.

In this regard, the following documents are particularly relevant:

1. Clinical evaluation plan, including clinical data available to date, of the product itself or similar
2. Publications about the product itself or similar products.
3. Critical evaluation of the data provided both from the clinical research carried out and from other scientific data.

Manufacturer License

Royal Decree 1591/09, Chapter II article 9:

In accordance with article 100 of Law 14/1986, of April 25, General Health, natural or legal persons engaged in the manufacture, import, grouping or sterilization of medical devices and the facilities in which they are carried out These activities will require a prior operating license, granted by the Spanish Agency for Medicines and Health Products. (...)
To obtain the authorizations referred to in the first paragraph of section 1, these will be requested from the Spanish Agency for Medicines and Health Products, which will study the documentation submitted and notify the resolution within three months from the date on which that the application and accompanying documentation have been entered in your registry. (...)

Royal Decree 1591/09, Chapter II article 10:

The request for a prior operating license must be accompanied by supporting documentation of the following requirements:

1. Availability of an organizational structure capable of guaranteeing the quality of the products and the execution of the appropriate procedures and controls.
2. Availability of adequate facilities, procedures, equipment and personnel according to the activities and products in question. In the case of concerted activities, the companies must declare the name and address of the subcontractors, describe the activities and means available to carry them out, provide the corresponding contracts and the manufacturing and control procedures used. Such concerted activities may only be carried out by entities that meet the requirements established for manufacturers, except for the prior operating license in the case of entities that do not meet the definition of manufacturer.
3. Availability of a technical manager, university graduate, whose degree certifies an adequate qualification based on the products in charge, who will exercise direct supervision of such activities. (...)
4. Availability of a document filing system to store the documentation generated with each manufactured or imported product and maintenance of a record of all products. The documentary file will be kept at the disposal of the competent authorities. (...)
5. Availability of a contact person for actions related to the Surveillance System. This designation may fall to the technical manager of the company.
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Business models

AI technology is the catalyst of business model innovations that disrupt industries and companies [3]. AI companies can be categorized based on the level of their business relying on AI as:

1. AI application provider (i.e. companies whose product simply could not function without AI at its core).
2. AI infrastructure provider (i.e. companies providing AI tools and infrastructure such as software and hardware).
3. AI adopter (i.e. companies or healthcare institutions using AI as part of a broader product or technology stack).

For AI solutions and products two different revenue models are considered: AI application as a service and AI infrastructure as a service.

For most AI application providers that develop sectorial solutions such as diagnosis systems, they normally generate revenue through the comoditisation of AI software. Many of these AI providers are startups running their business models based on application-as-a-service (AaaS) licensing model, by developing applications for specific use-cases for their clients. For

organisations (AI adopters) that decide to partner with AI technology start-ups to co-develop tailored-made solutions, a revenue-sharing or data sharing model could be adopted by both companies to meet a common interest. Both the AI technology provider and adopter can agree to build a proof of concept (PoC) and if it works, both parties share the benefits in the form of revenue or data proprietary. Implementing AI Application-as-a-Service, AI technology providers charge their customers with monthly running cost as well as operational support/training fees (i.e. annual subscription fee). They could also run a fee per study pricing model along with a perpetual licence and annual maintenance contract with their customers.
AI Application as-a service is a variation of the Software-as-a-Service (SaaS) model that would accentuate the role of sectorally competent AI companies. However, different from SaaS that normally is sold on a per-user bases, AIAaaS are priced by transaction or completed computation. The more work AI does, the more you pay for AI.

For organizations that are unwilling to build their own AI solutions or can't afford for budget reasons, they could tailor AI technology services provided directly from a third-party vendor and use them nearly immediately. In such case, the AI technology firms provide AI Infrastructure-as-a-Service by offering computational services such as infrastructure and pre- trained algorithms. They charge the usage of AI technologies based on API calls.

AI Infrastructure-as-a-Service is a model which extends and strengthens the existing business model that has gone through multiple "branding" stages from Outsourcing to Shared Services, to As-a-Service to Cloud – but remains constant. Generally, this model is based on moving from a company developing, maintaining, and operating their own technology services to a model where technology direction and operations is handed over to an external multinational company.

2.1 Case 1

The TRL of the up4Health technology is 6. The technology and results generated by CVC (such as software, databases, etc) are currently under review by IP experts to define the best IP protection strategy. We are conducting a patentability study and FTO analysis. Some of the results are already registered and we will expand protection of the technology under a legal team advise.

We are currently working on an extended market research report with Tekcapital and have drafted the first Business Plan with help of the Genesis Biomed consultants. We are currently working on the final version of the Business Plan, which includes preparation of final Business Plan and deck, guidance and fundraising support.

The whole project has been developed following the *Ethics Guidelines for Trustworthy AI*, which list seven key requirements for AI systems: (1) human agency and oversight; (2) technical robustness and safety; (3) privacy and data governance; (4) transparency; (5) diversity, non-discrimination, and fairness; (6) societal and environmental wellbeing; and (7) accountability. Since some of the data sources for our AI solutions may include sensitive personal information, we have consulted and follow the *Guidelines on Artificial Intelligence and Data Protection*.

2.2 Case 2

At the moment of writing this short report, the technology readiness level (TRL) for DeepLung is 6. For this reason, Eurecat conducted a regulatory assessment of the technology, which has been classified as a Class 2B medical device according to the ISO13485. The development of the technical file has also started in compliance with the guidelines outlined above. In compliance with efficacy and safety measures two new prospective clinical trials have been planned for further validation of the technology. Regarding HTA, we have conducted a cost-effectiveness analysis. The rest of HTA activities have also been planned.

Regarding IP, a full patentability analysis and freedom to operate (FTO) analysis have been conducted. The source code for the whole platform has been registered and copyrighted. It is expected that the final solution for DeepLung will be marketed as a SaaS.

2.3 Case 3 - CVC

Conclusions & Lessons Learnt

Developing a ML solution or product for healthcare is a long, time-consuming, and expensive process. These solutions being classified as medical devices must comply with different regulations right from the start of the development process. Compliance with data protection and privacy is the very first step. For this reason, it is extremely important to have approval from the Hospital's Ethical Committees, informed consents from patients signed, and proper data transfer agreements (DTAs) furnished between the hospital and project sponsor/data analyst. In this regard, it is extremely important that that all data is properly pseudonymized and, when some risk of reidentification is detected, data must be duly anonymized to guarantee patient's privacy and anonymity.

Data processing and model development is the most time-consuming task, which can be expedited by having access to quality data sources. Of course, the models built must be validated (QA) by health care professionals and stakeholders and even end-users.

Once the different ML modules have been developed and tested, it is important to start both the IP protection strategy through patentability and FTO analyses. At this stage is also important to start with the regulatory process to obtain a CE mark. For this reason, new confirmatory studies must be planned and executed with the acquiescence of, at least, the National Medical Agency or the European Medical Agency. In this regard, it is very important to draft the technical file outlining the methods of operation, safety and risk analyses, and documentation of all the results obtained so far in the development process. The technical file must also outline the necessary procedures for risk mitigation depending on the product classification. This phase also requires AI explainability for interpreting the results and minimizing biases. Also a suitable change-management and update strategy is required for the adoption of ML solutions in clinical settings.

Medical devices are classified according to the risk they impose on the patient. For example, a recommendation system giving information to a doctor about a certain illness is not the same as an automatic control for an insulin pump. Finally, the strategy for marketing strategy for the end-product must be defined and assessed.

Cited work

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[3] Directive (EU) 2016/943, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32016L0943

[4] https://ai.eitcommunity.eu/assets/docs/EIT-UrbanMobility-Emerging-AI-and-Data-Driven-Business-Models-in-Europe.pdf

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