Douglas *et al.*
Orphanet Journal of Rare Diseases (2022) 17:344
https://doi.org/10.1186/s13023-022-02476-6

Orphanet Journal of Rare Diseases

POSITION STATEMENT

Open Access

Social pharmaceutical innovation and alternative forms of research, development and deployment for drugs for rare diseases

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Abstract

Rare diseases are associated with difficulties in addressing unmet medical needs, lack of access to treatment, high prices, evidentiary mismatch, equity, etc. While challenges facing the development of drugs for rare diseases are experienced differently globally (i.e., higher vs. lower and middle income countries), many are also expressed transnationally, which suggests systemic issues. Pharmaceutical innovation is highly regulated and institutionalized, leading to firmly established innovation pathways. While deviating from these innovation pathways is difficult, we take the position that doing so is of critical importance. The reason is that the current model of pharmaceutical innovation alone will not deliver the quantity of products needed to address the unmet needs faced by rare disease patients, nor at a price point that is sustainable for healthcare systems. In light of the problems in rare diseases, we hold that re-thinking innovation is crucial and more room should be provided for alternative innovation pathways. We already observe a significant number and variety of new types of initiatives in the rare diseases field that propose or use alternative pharmaceutical innovation pathways which have in common that they involve a diverse set of societal stakeholders, explicitly address a higher societal goal, or both. Our position is that principles of social innovation can be drawn on in the framing and articulation of such alternative pathways, which we term here *social pharmaceutical innovation* (SPIN), and that it should be given more room for development. As an interdisciplinary research team in the social sciences, public health and law, the cases of SPIN we investigate are spread transnationally, and include higher income as well as middle income countries. We do this to develop a better understanding of the social pharmaceutical innovation field's breadth and to advance changes ranging from the bedside to system levels. We seek collaborations with those working in such projects (e.g., patients and patient organisations, researchers in rare diseases, industry, and policy makers). We aim to add comparative and evaluative value to social pharmaceutical innovation, and we seek to ignite further interest in these initiatives, thereby actively contributing to them as a part of our work.

Keywords: Social pharmaceutical innovation, Orphan drugs, Rare diseases, Therapeutic research and development, Social innovation, Policy, Patient organisations

Background

The rare disease field is host to a growing number of initiatives that engage in pharmaceutical innovation in various and distinct ways. The initiatives include novel types of research and development collaborations (e.g.,

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public–private partnerships), decentralised forms of manufacturing, alternative regulatory and reimbursement schemes, etc. They are of significance due to their role in addressing some of the well-documented challenges of availability, accessibility, affordability, and acceptability of treatments for rare diseases. For instance, the identification of prospective biochemical or even genetic targets and eventual development of compounds for these targets is inefficient in most drug innovation processes, let alone in rare diseases [1, 2].

Innovation for rare diseases is also associated with unique challenges. Historically, one of the reasons for the lack of innovation lies in small patient populations making investment less attractive to companies, and scientists. While market rationale for the development of niche products may be shifting [3], intellectual property rights and secrecy are thwarting information sharing, collaboration, and thereby research and innovation [4], and "national patent protection alone has not born out to stimulate domestic innovation" [5]. Another challenge in the rare disease space are the high prices associated with these products, with many of the most expensive drugs in the world targeting rare diseases [6]. There are numerous reasons extolled for the high cost of these drugs (e.g., the small market size, the high cost of research and development, high failure rates, industry's need to recoup high-risk investments, amongst others). Fundamentally, however, this is an industry, and pharmaceutical companies are obligated to their shareholders to increase profits. Finally, there is a stark evidentiary mismatch between industry submissions and the existing regulatory and Health Technology Assessment structures. This mismatch causes delayed access to medicines and sometimes to poor coverage decisions.

While this is not an exhaustive list of the structural problems facing the pharmaceutical industry and its regulatory environment, it is evident that there are -at the very least- constraints on the current system to deliver on the needs of rare disease patients. Importantly, while some challenges are experienced differently globally (i.e., higher vs. lower and middle income countries), many are also being expressed transnationally, which thereby suggests systemic issues. Therefore, we pose that the current model of pharmaceutical innovation alone will not deliver the quantity of products needed to address the unmet needs faced by rare disease patients, nor at a price point that is sustainable for healthcare systems.

In the face of these challenges, we are observing a significant number of innovative initiatives in pharmaceutical innovation that depart from -and sometimes disrupt- the entrenched, traditional, linear, industry-led model of innovation [7]. In many jurisdictions, rare disease patients, patient organisations, and patient advocacy groups play an increasing role in all phases of drug research and licensing [8, 9]. Transformations are also underway in drug manufacturing and production processes, with pharmacists increasingly compounding medications and in-hospital production of drugs for individuals or groups of patients with rare disease [10–12]. At the regulatory level, an increasing number of outcomes-based risk-sharing agreements have emerged to help manage the uncertainty of drug efficacy through further collection of data. Similarly, finance-based risk-sharing agreements have worked to manage the impact of drugs for rare diseases on the sustainability of health systems through price controls. Risk-sharing agreements have also become more prevalent after market approval, in the form of extended pharmacovigilance procedures and the collection of real-world evidence to help inform coverage decisions [13–19].

These initiatives in pharmaceutical innovation just mentioned have in common that they involve several societal stakeholders, explicitly address a higher societal goal, or both. Examples include M4K Pharma, a Canadian-based organisation forwarding a new business model "that aims to align diffuse academic and industry research into a collaborative open science drug discovery programme" [20]. It is currently focused on research and development (R&D) of a treatment for a rare paediatric brain cancer through diffused intrinsic pontine glioma (DIPG) [21]. A second example is the international platform 'myTomorrows', which seeks to connect patients with unmet medical needs to expanded access programmes and ongoing clinical trials [22]. A third example from later in the life-cycle of rare disease treatments is the increasing number of Latin American countries that are making use of expedited regulatory review and/or reliance pathways that use data from other jurisdictions to expedite approvals [23].

While many of the foregrounded initiatives of pharmaceutical innovation involve a wide range of stakeholders, they are often unconnected from one another and exist in a fragmented landscape. Moreover, significant variation exists in terms of organisation, and the societal goals of these initiatives range from addressing specific development barriers for particular patient populations to striving for broader systemic change. As a result, we pose that there is an urgent need for re-thinking innovation and that more room should be provided for new innovation pathways. Our position is that principles of social innovation can be drawn on in the framing and articulation of such alternative pathways, which we term here *social pharmaceutical innovation* (SPIN), and that it should be given room to be experimented with. We will use our background in the social sciences, law, and public health to develop an interdisciplinary approach to analyse -and

where possible support- these initiatives in collaboration with the people and organisations involved.

To be sure, SPIN initiatives are themselves rare, that is: exceptions to the existing bio-pharma-led model for innovation dominating the landscape. That said, we see room for more alternative approaches within that innovation landscape, and interesting initiatives are underway that are doing things differently. The research program that we are advancing in the below suggests that we can learn from -and support- those initiatives through systematic interdisciplinary social science research grounded in social innovation. Our objective here is to outline that research program while setting the stage for future empirically-derived policy recommendations to emerge from on-going research.

Towards social pharmaceutical innovation

Pharmaceutical R&D in rare diseases as an interactive and multi-faceted process

Over the years, studies of science, technology and society (STS), law and the emerging field of innovation studies have documented the inseparability of social and technical aspects of the world and how they co-develop. Extensive research across a wide range of fields suggest that technological change is best understood when we analyse it as evolving in multi-directional and iterative forms rather than a linear manner. As such, the evolution of new technologies shows the essential -yet variable- role of involved social groups in shaping innovations [24–26]. Even in the context of pharmaceuticals, where process stages are tightly structured and heavily regulated, there is not one predetermined channel or finite manner through which drugs are researched, developed, and brought to market. On the contrary, in the area of pharmaceuticals numerous routes to innovation can and do exist [27–31]. Understanding the variety and form of these pathways requires an understanding of the social and technological factors that shape them.

Quite clearly then, science and technology do not exist in a social, historical, cultural, political, or economic vacuum. Institutional arrangements, laws, policies, economic and ethical assessments vary from one country to the next and impact how and which biotechnologies are developed [32]. The perspective of innovation processes being non-linear and interactive works to demonstrate how these factors influence emerging forms of pharmaceutical innovation in the rare disease space. At the same time, innovations in health technologies and medical science also impact the manner in which our societies are organised, how we relate to each other, and how we see ourselves. Examples here include ending diagnostic odysseys through advanced genomic technologies that can have both positive and negative effects for rare disease patients and their families by transforming an undiagnosed child into a rare disease patient, thereby perhaps ending hope of recovery while also facilitating connection to peer groups and community building [33]. Another example is how variable access to drugs for rare diseases can create or exacerbate (social) inequalities between rare disease patients, as well as divisions with patients receiving treatment for more common conditions [34, 35].

Seen this way, science, technology, society, and social change should be analysed as being co-produced [36], and that obviously includes the changing field of rare diseases where we have undertaken considerable research [25, 37–48]. Our interdisciplinary approach to co-production is rooted in academic disciplines of STS, law, public health, and innovation studies. We hold that a focus on co-production is critical to develop a broader, more comprehensive understanding of how novel initiatives are seeking to address some of the challenges associated with the development of drugs for rare diseases and identifying why some of them succeed whereas others struggle.

From social innovation to social pharmaceutical innovation

With the view of innovation being co-produced, one particularly fruitful concept for developing an understanding of these novel initiatives in rare disease research is *social innovation*. Social innovation is especially used in the context of so-called 'wicked problems', such as climate change, increasing life expectancy and associated health and social care costs, and growing inequalities. These problems are all characterized by complexity, interconnectedness, and "multiple and contradictory analyses and diagnoses" [51], which are certainly recognisable in the rare disease field. Inability to address these problems is accompanied by "a collapse in trust in the status quo—as established models and social relations have increasingly failed to deliver well-being for many" [51].

Social innovation can be defined as "the development and implementation of new ideas (products, services and models) to meet social needs and create new social relationships and collaborations" [49]. Westley and Antadze expanded upon this by noting that:

> *"Social innovation is a complex process of introducing new products, processes or programs that profoundly change the basic routines, resource and authority flows, or beliefs of the social system in which the innovation occurs. Such successful social innovations have durability and broad impact" [50].*

At its core, social innovation (SI) "is aimed at improving human well-being" [49]. It is orientated towards serving social needs and towards building resilience. It is both

innovation in, and innovation through, new arrangements and ways of organising. Thus, SI is concerned with both actions and their effects, and the way in which an outcome is achieved matters in that "innovation is both a process and a product" [56]. It is important to note that SI is not new; rather, there is a long history of processes and practises operating under different labels that can be traced back to the eighteenth [52] or nineteenth century [53]. Some SI scholars have argued that it is, in fact, "a common dynamic of human history" [54].

While (whole) systems thinking is of use and value for understanding the dynamics related to complex and interconnected phenomena like the environment [55]. SI is often studied on a project or organisational level, which aligns well with our focus on initiatives in the rare disease field. At the same time, SI projects are heavily linked with various parts of (innovation) systems [51]. SI is generally needs-led or demand-led rather than supply-driven, which translates to significant roles for users and citizens in innovation processes [49]. For this reason, SI can be characterised more as "grass roots", "bottom-up" and community-supported compared to more conventional forms of innovation [56]. Innovation that is bottom-up in nature, with a significant role played by users, flourishes within open and collaborative approaches [56]. Openness, in this context, refers to the more freely sharing of knowledge, a more communal approach to the ownership of knowledge, as well as disciplinary openness in which different approaches can be integrated together towards problem solving [49]. It is often seen as critical that diverse actors from a broad range of stakeholder groups or sectors are involved in exchanging ideas and values towards the generation of solutions [57].

When diverse stakeholders are brought together in open and collaborative problem-solving initiatives, much stands to be gained in terms of the products or outcomes of these collaborations [58]. In doing so, SI is as much directed at capacity building and empowerment of users and citizens [57] as it is to tailor-made results to specific needs instead of mass-produced solutions to more general problems [49]. Importantly, products resulting from SI are not solely market-driven; to the contrary, "social innovations [often] literally serve demands which neither the state nor markets would or can meet" [56]. This is not to say that SI does not involve businesses or private capital; rather, "new business models [are emerging] that meet the needs of underserved populations" [58]. Here capital investments are not exclusively focussed on maximising their returns, and businesses can be involved in collaborations. To this end SI is socially orientated, it is directed at developing resilience among institutions, networks, and systems, as well as "enhance[ing] an individual's capacity to act" [49] based on values of solidarity and inclusiveness.

Well-known examples of social innovation are technologies like M-PESA, which is a form of mobile banking used in low- and middle-income countries allowing users to easily save and transfer money in the absence of conventional bank accounts. Scholars consider M-PESA a social innovation on the institutional level as it reconfigures market structures and patterns [51]. In fair trade, another well-known social innovation, marginalised farmers are connected to ethically-minded consumers through novel product distribution processes that seek to reduce global inequality and deliver additional social value [59]. Prominent examples of health-related social innovation projects include the deployment of community-driven diagnostic techniques for malaria testing via schools in Malawi, cervical human papillomavirus (HPV) sample self-collection in Peru, and crowdsourcing human immunodeficiency virus (HIV) testing in China [60], and the world's largest provider of cataract surgery in India (i.e., Aravind Eye Care) that provides "low-cost products and services to the poor…[by combining] a hyper-specialised division of low- and high-skilled labour that is unheard-of in costly hospitals of the industrialised world" [61]. SI may also have indirect health effects, such as projects contributing to Sustainable Development Goals that seek to improve overall health and well-being [62–64].

Defining social pharmaceutical innovation (SPIN)

The novel practices we are observing across the R&D lifecycle of rare disease drugs are creating opportunities for re-envisioning pharmaceutical innovation through what some SI scholars refer to as the "adjacent possible" [54, 65, 66]. This term refers to "the range of alternative social arrangements [which are] just beyond the horizon of prevailing practice" [54]. Social pharmaceutical innovation (SPIN) can be regarded as a way to both more fully understand these "adjacent possibles" in drug development, as well as contribute to its further progress.

To explore SPIN, we need a working definition. We understand SPIN as novel forms of collaborative processes, programs, policies, procedures and/or designs involving diverse sets of actors that break with conventional pharmaceutical innovation practices for the production of safe, effective, and accessible interventions that address unmet societal needs of rare disease patients and that are not primarily market driven. Similar to SI, we see SPIN pertaining to both transformations in processes as well as in novel outcomes; however, these two concepts differ in the respect that we see SPIN as an emerging techno-social phenomenon and a research object rather than an analytical perspective. We see SPIN as a 'working concept', both in terms of the work it carries

out as a heuristic device that aids in framing research and asking pertinent questions concerning transformations in pharmaceutical R&D, and in terms of being a concept 'in work' in terms of its evolving nature. As such, we anticipate our definition of SPIN to develop through further empirical investigations, conceptual elaboration and engagement with stakeholders.

By framing novel initiatives in rare diseases in terms of SPIN, we aim at developing a better understanding of the field's breadth as well as exploring contributions to—and further opportunities for—change ranging from the clinical to system levels. Furthermore, we seek to identify commonalities between initiatives in a fragmented landscape and this lens can be instructive in making sense of the organisational processes and goals of rare disease initiatives. In doing so, a SPIN framing also contributes to creating/identifying a common language to understand phenomena and enables communication about them, thereby making innovative processes and products more visible, legible, and comprehensible.

Social pharmaceutical innovation: a tentative typology

To build-up this project and to facilitate its further collaborative development, we outline three types of SPIN that our case studies deal with, which brings a range of important questions into focus. These different types of SPIN reflect diverse points throughout the life-cycle of pharmaceutical research, development and deployment, which allows us to examine innovation challenges in rare diseases in terms of whole systems. Furthermore, these types of SPINs that we outline represent initiatives that are tentative solutions to some of the challenges facing rare diseases.

The first type of SPIN to consider are *novel R&D partnerships across the public, not-for-profit and private sectors*. These forms of SPIN exemplify the critical role that collaboration stands to play in rare disease research in terms of creating networks, connections, and cooperation, which includes the importance of patient empowerment in developing and steering research based on their needs. These partnerships can, and do, cover the full range of research from the very upstream developments of novel technological platforms, systems, and policies for the sharing of genomic data for gene discovery to further diagnostics (e.g., Canadian Genomics4rd research platform [67] or European Share4Rare platform [68]), partnerships that focus on N-of-1 trials (i.e., trials on a very small number of patients, and even on a single patient) [69] and the development of new drugs (e.g., Inspire2Live, a Dutch cancer patient organisation in the process of co-creating a clinical trial [70]), to the repurposing of existing drugs [71]. Other partnerships have developed around clinical research that combines clinical data and observations reported by patients and/or their representative organisations when the clinical outcomes are difficult to assess due to the rarity of the disease. Examples of this can be seen through the French Muscular Dystrophy Association (AFM) who argue that classic endpoints do not capture all benefits that treatments bring to patients, which are not listed as an endpoint despite being very valuable for patients (e.g., some treatments for neuromuscular diseases may help patients move one finger and manipulate the controls of their electric wheelchair). Central questions raised in understanding this first type of SPIN concern the nature of multi-sectoral partnerships in question, in terms of what they do and what they aim for. Also critical to an appreciation of this form of SPIN is describing how the various actors involved frame the problems and causes they seek to address (e.g., right to health, social justice, equity, unduly high profits for companies), and how they reflect on their role in what they are doing, why they are doing it, and how their practices align with their initial motivations and incentives. Understanding these partnerships means understanding how they organise work and activities relative to the medical, practical, regulatory, and politico-economic environment, and the obstacles they face as they proceed.

A second type of SPIN we have started to study is the development of *alternative forms of provision and licensing*. These include magisterial preparations (i.e., medicines prepared by pharmacists based on prescriptions for unmet needs like lower dosages for children, but also when negotiations for lowering a drug's price fail), public sector manufacturing (e.g., when the state or a public–private partnership takes the lead in producing a treatment in their own facilities) (72), early access schemes [73] and compassionate use (e.g. the provision of promising experimental treatments before they get market approval in the context of urgent medical needs), and adaptive pathways (e.g. the European Medicines Agency's approval under exceptional circumstances and conditional marketing authorisation). In exploring these alternative forms of provision and licensing, the nature of scientific and economic evidence produced throughout SPIN is brought forward, as well as the sort of knowledge this evidence is based upon. Critical here is understanding how evidence is debated between the various actors involved, in particular when evidence is brought in by patient organisations, and the extent to which this evidence challenges the statistical reasoning that underlies clinical trials and much Health Technology Assessment. Another question is whether and how actors from different institutional backgrounds (e.g., public, private, community) are able to align their incentives and activities in novel collaborative arrangements?

The third type of SPINs studied are *alternative regulatory frameworks for coverage*. Initiatives for new medico-economic Health Technology Assessment procedures that consider the social value of drugs for unmet needs [74, 75], as well as new pricing [76] and reimbursement schemes negotiated between companies and public authorities to lower the prices of certain drugs, are some examples [19, 77, 78]. Here the focus is on the nature of regulatory and institutional change that SPIN contemplates, or drives. In particular, interest centres on how these alternative regulatory frameworks for coverage disrupt the traditional linear model of pharmaceutical innovation, and in some instances conjointly address issues of availability (e.g., R&D and clinical trials), accessibility (e.g., pricing and coverage), and acceptability (e.g., safety vs. mortality of disease and equity issues). It is important to highlight the role of modern democracies to create legal and institutional responses to guarantee innovation and accessibility of pharmaceuticals for rare diseases.

While not an exhaustive typology, these diverse forms of SPIN demonstrate that innovations are needed -and are underway- throughout the research and development life-cycle. Tackling the challenges facing pharmaceutical R&D for rare diseases requires a whole system lens to identify dynamics related to early stage research and development, production, and manufacturing, as well as the coverage and payment issues raised by questions of "value" that override downstream issues of pricing and coverage [79]. Quite clearly, the nature of partnerships in early-stage research and clinical trials impinges on how products stand to be manufactured, brought to market and paid for.

Furthermore, it is also quite clear that the answers to the questions associated with the three different types of SPIN outlined above vary across the countries of the cases explored by the respective research teams on which our project builds (i.e., Brazil, Canada, France and the Netherlands). Discussion of similarities and differences between cases -as well as national contexts- on the basis of three cross-cutting issues helps to further articulate the integrated framework our work seeks to promote. It is a discussion of those cross-cutting issues that we now turn to in the development of our analytical framework for SPIN.

Towards an analytical framework for social pharmaceutical innovation

Explorations into different types of SPIN necessitate analysis on at least three cross-cutting issues. The first is an understanding of the diverse problem-framings and goals of SPIN initiatives. This includes the national and transnational debates surrounding drugs for rare diseases, as well as how these debates are framed, and through which media they play out. In part, this entails understanding how various actors frame the problems and the causes that their innovative efforts seek to address, and what they attempt to accomplish through new forms of collaboration. What issues do particular groups bring into the spotlight, and how do they seek to address them through their SPIN initiative? Is it possible to identify areas of convergence or divergence of problem-framings and/or goals within these novel forms of collaborative research? Are actors working towards addressing the same issue or is the collaboration a marriage of convenience? In forms of SPIN that involve alternative forms of provision and licensing, analytical questions include how intellectual property (IP) regimes are being framed. Our approach seeks to understand how a SPIN would approach IP: as a driver for innovation, or as a constraint that is locking-in particular modes of manufacturing and delivery? Furthermore, interest here centres on how SPIN projects are approaching issues of local capacity, both in terms of the capital, technology, and facilities required for the production of advanced products that target rare diseases (e.g., cell and virus manufacturing) as we as human capital, personnel, and advanced training needed to actually carry out the manufacturing work. An appreciation of these problem-framings is not only instructive for understanding the goals of SPIN initiatives, but also to understand if and how much room there is for differential IP regimes and alternative manufacturing capacities. For SPINs targeting alternative regulatory frameworks for coverage, understanding how participants see rare disease policy initiatives across different constituencies is also critical for identifying and characterising the target of their policy interventions. Some alternative frameworks for coverage have recently been attempted to advance equity in terms of access across European member-states as well as between Canadian provinces. Other innovative initiatives target the cost containment on drugs for rare diseases and to ensure the sustainability of health systems more broadly. Alongside the characterisation of these policy goals, we also investigate how bureaucratic and political frameworks constrain novel forms of R&D and medicinal products. Could alternative regulatory frameworks for coverage disrupt the traditional linear models of pharmaceutical innovation? How? To what extent, but also why not? Answers to such questions are key to fully understanding the forms and limits of social pharmaceutical innovation and to properly articulate policy recommendations for (experimentation with) SPIN initiatives.

The second key cross-cutting issue is processes: how are SPIN constituted and through what processes and factors are they adjusted and actually carried out? What role does the decentralised and distributed

character of these SPIN processes play in this, and how are collaborations organised and managed? Careful consideration must be given to when, where and how multi-sectoral partnerships emerge, and particularly when patient organisations intervene and/or are mobilised for the design and conduct of SPIN. Studying SPIN means attending to the processes through which patients and external publics and media are involved. It also requires analysing how nascent forms of R&D produce new forms of evidence that challenge existing regulatory structures and motivate institutional reform and change. Through such R&D new forms of SPIN may link up with the associated battles and debates over new forms of evidence. This is especially likely when evidence is brought in by patient organisations or investigator-initiated trials or registries. Here, research focuses on the extent to which this evidence challenges the statistical reasoning that underlies clinical trials regulations and Health Technology Assessments that are central to the authorization of drugs for rare diseases. Subsequent analysis along the life-cycle of pharmaceuticals then focuses on the nature of regulatory and institutional change that SPIN contemplates or drives, and in some instances, overturns. Significant variation exists across constituencies and regulatory domains with regards to patient access and health insurance coverage. Health costs coverage regimes, risk sharing agreements and alternatives to existing systems that can be understood as SPINs are topics to be covered in our research. How these agreements are negotiated and carried out is by no way uniform, which offers fertile ground for cross-national learning and comparative analysis of the socio-institutional character of SPIN processes, for which input from the rare diseases field is most welcome.

Finally, SPINs must also be examined and held to account for their outcomes and/or products. Critical questions must be asked of the extent to which SPINs are delivering on their promises: What successes may be claimed? What can be learned? How to improve the track record of SPINs in targeting rare diseases? How and where have SPINs reorganised work and activities relative to the medical, practical, regulatory and politico-economic environment? When and how can activities be aligned better, and sincere collaborations be stimulated? In setting up partnerships, what obstacles do SPINs face? In summary: Are SPIN initiatives conjointly addressing the issue of availability (R&D and clinical trials) and the issue of accessibility (pricing and coverage)? What are the transformative prospects for the rare disease field as a whole?

Through these three cross-cutting lines of inquiry we may begin to think about ways of systematically analysing, assessing and ultimately understanding the different types of SPIN as introduced in "Social pharmaceutical innovation: a tentative typology" section. We invite collaborative research with stakeholders in this area on these three cross-cutting lines of inquiry. Questions that can be posed are suggested in Table 1 below, and together with initial points of discussion addressed in the section "Initial points of discussion relating to social pharmaceutical innovation", a SPIN research program can be developed as a way of stimulating more thought and collaborative research in this area.

Initial points of discussion relating to social pharmaceutical innovation

Through the framing of examples of SPIN in the rare disease space, important differences are emerging between seemingly identical cases and across contexts and constituencies. The first type of difference relates to the diversity of initiatives. As we have argued, SPINs cannot easily be divided up into discrete sets of practices, but rather amount to a series of distinct and different initiatives and dialogues ranging from more inclusionary forms of research and development to policy changes at the regulatory or health systems level. This rich arena offers ample and significant opportunities to learn how different constituencies engage with and address challenges relating to drugs for rare diseases. This diversity prompts social scientific methodological reflection in terms of our topics of study (i.e., actions, processes or discourses). Related to this point of diversity of SPIN is the fact that writ-large differences exist depending on global, national or even regional contexts. We are observing that capacities for collaborative research and development initiatives differ between lower, middle, and higher income countries. Political stability, economic and industrial development, social inequalities, corruption, among other factors, have a direct impact on the country's capacity for social pharmaceutical innovation. At the same time, inequalities and hurdles can also facilitate creative social innovation. Furthermore, constitutional and policy arrangements of individual countries are also proving to be significant mitigating factors in the success of—let alone possibility for- some forms of SPIN.

The second point to critically reflect on as part of what we do concerns the nature of participatory research activities in terms of who is included in such endeavours, who is left out, who decides who participates, and to what end? Here, we will focus our discussion on the role of the government/authorities and their legitimacy vis-à-vis the pharmaceutical and biotech sectors that have usually driven research and development in this area. Related to discussions about inclusion are points related to prioritisation: why are some kinds of SPIN undertaken

Table 1 Analytical questions to ask about social pharmaceutical innovations

LINE OF ANALYSIS	TYPE OF SPIN		
	Novel R&D partnerships across the public, not-for-profit and private sectors	**Alternative forms of provision and licensing**	**Alternative regulatory frameworks for coverage**
Problem-framing & goals of SPIN initiative	How do various stakeholders involved frame the problems -and their causes- they seek to address?	How are IP regimes locking in particular modes of manufacturing and provision? What room is there for distinct forms of IP regimes and manufacturing capacities within the national or regional context in which SPINs are taking place?	How are regulatory and political frameworks constraining novel forms of R&D and emerging forms of medicinal products? How do alternative regulatory frameworks for coverage disrupt the traditional linear model of pharmaceutical innovation?
Nature of SPIN processes	What is the nature of multi-sectoral partnerships in question (e.g., distributed, decentralised, transdisciplinary), in terms of what they actually do and what they aim for?	How is evidence debated between the various actors involved? How do diverse forms of evidence challenge the statistical reasoning that underlies clinical trials and health technology assessment?	What is the nature of regulatory and institutional change that SPIN contemplates or drives?
Outcomes of SPIN activities	How have partnerships (re)organised work and activities relative to the medical, practical, regulatory and politico-economic environment? How lasting are the R&D partnerships facilitated by SPINs? Are they one-off cooperatives or more enduring relationships?	What are the outcomes of alternative forms of provision and licensing in terms of changes in access and availability to drugs for rare diseases?	How have alternative policy and regulatory frameworks facilitated transformations in addressing the issue of availability (i.e., R&D and clinical trials) and/or the issue of accessibility (pricing and/or coverage)?

rather than others? Why is it that advanced therapeutics such as gene and cell therapies seem to be prioritised over other types of medicine? Why do particular rare diseases draw more attention and galvanise novel research partnerships or negotiate managed access where others do not? To be sure, scientific and technical features figure into the answers to some of these questions, which our consortium considers alongside socio-cultural and political-economic drivers. How do such features and drivers relate or get related?

The third point raised in our analysis of SPIN has to do with the extent and degree of change they enable on a systemic level. Within the SI literature, it is argued that "[t]o achieve broad, lasting change, social innovations must cross multiple scales" [54]. We are indeed observing scale-up difficulties in some instances of SPIN (e.g., with hospital-based or public sector manufacturing of cell therapies). Such difficulties are the result of existing regulations, push-back from incumbent actors and/or the complexity of de- and re-contextualising solutions that work well in specific settings. However, this raises broad strategic questions for stakeholders about outcomes, success, and possible failure. How to challenge and change the system and how radical system change may be achieved? Is it the case that SPIN must have lasting system impacts if -for example- they are able to secure medicine for (a) patient(s) that might not otherwise be treated? How does one evaluate more micro-level interventions that might be transitory against endeavours that seek more system-wide change? Might we see these 'smaller' interventions as kernels of radical novelty (perhaps remaining mostly within the realm of exploratory scientific research) which should be cherished as potential future niches of change? Relatedly, should all niche initiatives have the ambition to diffuse or scale up? Furthermore, should more ephemeral SPIN initiatives be considered failures due to their lack of lasting change, or is there nuance in initiatives that do not scale up or even do not fully work out?

These points of discussion require careful consideration from multiple angles, which is a further reason why we actively seek collaborations with actors within these emerging initiatives in the rare disease space and input from those communities on the further development of future research agendas and aims.

Conclusion

Pharmaceutical innovation is highly regulated and institutionalised with innovation pathways that are firmly established. As deviating from these innovation pathways is thus difficult, the currently dominant model of pharmaceutical innovation as such will not deliver the quantity and quality of products needed to address the unmet needs faced by rare disease patients, nor at a price point that is sustainable for healthcare systems. In light of the problems in rare diseases, our position is that there is a need for re-thinking innovation, that room should be provided for new innovation pathways, and that principles of social innovation can be drawn on in the framing and articulation of such alternatives. Changes are already underway around rare diseases related to pharmaceutical R&D, the organisation and delivery of health care, and increasing participatory and stakeholder-driven citizen/patient engagement. Taken together we have termed these: *social pharmaceutical innovation.* The initiatives we observe are underway, and while they may not supplant dominant modes of pharmaceutical R&D, they may offer viable alternative innovation pathways that provide novel and prospectively beneficial outcomes for the existing challenges and hurdles in this area. Building on research and practice in social innovation, our perspective on these developments seeks to add, first, explanatory value of what is taking place from a broader socio-technical perspective; second, comparative value of what has and has not worked in other contexts (including experiences with challenges and barriers within and between lower, middle, and higher income countries); and third, evaluative value concerning the outcome of these initiatives and what they have been able to achieve vis-à-vis their goals and impacts on dominant pharmaceutical R&D practises. Taking stock of these developments works not only to unite these disparate innovations, but may also provide a better and distinctive socio-technical analytical framework for understanding, explaining, and helping to improve their impacts and implications. As outlined in Table 1, by formulating these developments in terms of *social pharmaceutical innovation*, critical research questions emerge about the problem-framing and the goals through which SPINs work as well as the nature of SPIN processes and outcomes.

We see these questions and our perspective as a part of an ambitious agenda for future research that we want to contribute to and with which we hope to draw in others to do the same. We invite collaboration within this agenda, and offer our social science perspective. Furthermore, by naming and framing these activities in terms of *social pharmaceutical innovation*, we not only seek to ignite further interest in these questions but also hope to actively contribute to them through the development of shared language and concepts. We also seek to contribute by engaging with the organisations and stakeholders we study to discuss our findings. As part of this, we will organise an outreach conference on the 9th and 10th of March, 2023. There we will share the preliminary findings of our research on a selection of case studies of different types of SPINs from our respective countries, and

receive feedback from stakeholders in this space on the policy recommendations we are developing in support of SPIN.

To make an impact, it is important to analyse how the differentiated dynamics of broader fields affect and structure opportunities and limitations of what can be achieved and the disagreements and struggles about what (can)not be achieved. Studying this in depth requires collaboration with actors striving for change who are involved in concrete projects as well as with experts from a variety of disciplines. We invite and welcome such collaborations, and offer our interdisciplinary expertise and perspectives there within.

Acknowledgements
We acknowledge the support of funding agencies and the Trans-Atlantic Platform in support of our work.

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CMWD is the corresponding author. He made substantial contributions to the conception and design of the work and drafted the work and substantively revised it. He approved the submitted version (and any substantially modified version that involves the author's contribution to the study). He agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. FA made substantial contributions to the conception and design of the work. 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Funding

This project is made possible through the Trans-Atlantic Platform for Social Science and Humanities that brings together public research funders from South America, North America and Europe. The Social Pharmaceutical Innovation project is file no.: 463.18.238. The Brazilian component of this study is funded by the Fundacao de Amparo a Pesquisa do Estado de Sao Paulo Process number 19/02519-0. The Canadian component of this study is funded by the Social Sciences and Humanities Research Council of Canada file no.: 2002-2019-0006. The Dutch component of this study is funded by the Dutch Research Council (NWO) project number: 463.18.238. The French component of this study is funded by the Agence Nationale de la Recherche (ANR) project number: ANR-19-ISOC-0001-03.

Availability of data and materials

Not applicable. This manuscript does not contain any data.

Declarations

Ethics approval and consent to participate

Not applicable. As a position statement no research using animals or people was used in the production of this work.

Consent for publication

Not applicable. This manuscript does not contain data from any individual person.

Competing interests

FAM is currently employed at Health Canada. There are no other competing interests.

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Received: 28 February 2022 Accepted: 13 August 2022
Published online: 05 September 2022

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Publisher's Note

Valdecilla Instituto de Investigación Sanitaria IDIVAL

New types of Artificial Intelligence in health: ethical and legal challenges

Joaquín Cayón

DERECHOS DIGITALES

Financiado por la Unión Europea NextGenerationEU

red.es

Plan de Recuperación, Transformación y Resiliencia

1

IA OPPORTUNITIES

Huge datasets proccessed by algorithms

and sophisticated data models are allowing many opportunities

(a) Healthcare sector

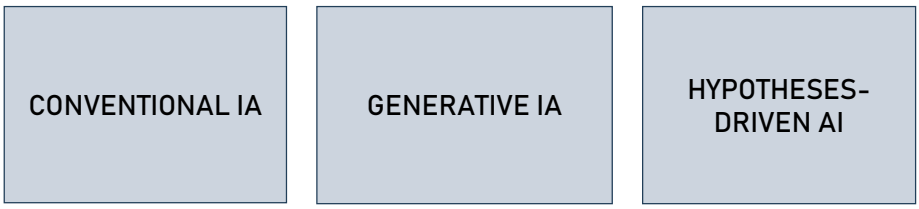
- *predictive medicine*: improvement of prevention and diagnosis
- *personalized medicine*: improvement of medical treatments

2

(b) Pharmaceutical sector

- **New drugs´ discoveries:** The pharmaceutical industry can use Big Data to qualify a particular drug for a patient based on the his/her genetics, diseases and lifestyle.
- **Avoiding adverse events from medicines**
- **Optimizing clinical trials**: More effective
  - Using Big Data reduce the number of clinical trials (and expenses).
  - Patients can be selected for trials according to certain prerequisites found through Big Data analytics.
  - Researchers can monitor participants in real-time.

3



Convencional AI

↓

Gen-AI

From existing data

↓

It creates an UNIQUE and ORIGINAL content

Text, Image, Audio, Video or Code

NOV 2022

5

And evolution continues….

Hypothesis- driven AI

MAYO CLINIC

Inside Precision Medicine › Oncology › Mayo Clinic's Hypothesis-Driven AI Can Improve Treatment Strategies

Mayo Clinic's Hypothesis-Driven AI Can Improve Treatment Strategies

April 17, 2024

A new class of artificial intelligence (AI) called hypothesis-driven AI, invented recently by Mayo Clinic researchers, offers an innovative way to discover the complex causes of cancer and improve treatment strategies.

Review > Cancers (Basel). 2024 Feb 18;16(4):822. doi: 10.3390/cancers16040822.

The Rise of Hypothesis-Driven Artificial Intelligence in Oncology

Zilin Xianyu [1], Cristina Correia [1], Choong Yong Ung [1], Shizhen Zhu [1 2], Daniel D Billadeau [1 3], Hu Li [1]

Conventional AI challenge: maximising information from large **databases.**

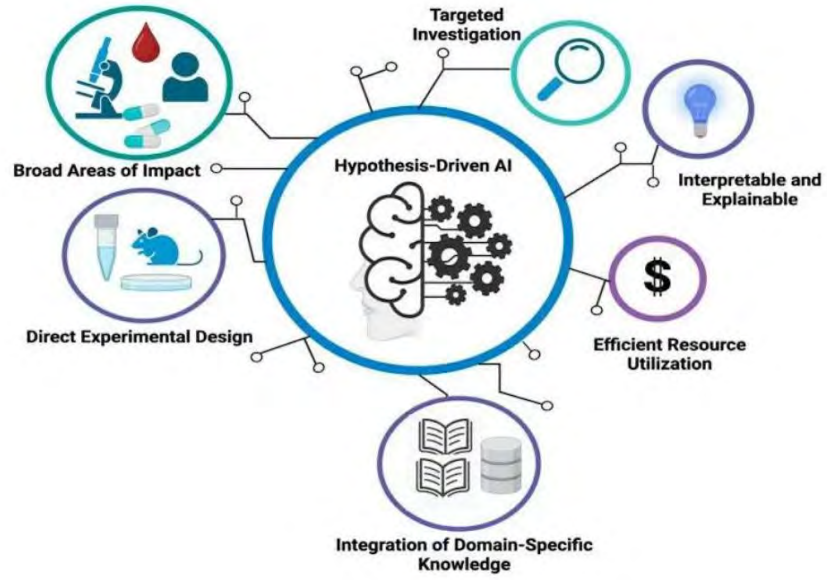
Hypothesis-driven AI challenge: optimise understanding of a disease, by incorporating **scientific hypotheses** into the algorithm

7

Benefits of hypothesis-driven AI:

- Focuses on specific hypotheses or research questions;
- Leverages existing knowledge to find previously missed connections
- Is more interpretable, providing results that are easier to understand than with conventional AI;
- Requires less data and computing power;
- Helps scientists to test and validate hypotheses by incorporating hypotheses

8



Executive Orden on the Safe, and Truestworthy Development and Use of AI (2023)

- Standardised evaluations
- Promotion of mechanisms for the protection of civil rights and freedoms

Data Protection and Digital Information Bill (2024)

- Art 17, Assesment of High Risk Procesing

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

Framework Convention on AI Human Rights, Democracy and the Rule of Law(2024)

- Measures taken to: Identify, prevent, assess and mitigate potential risks.
- Measures in relation to the use of AI where it poses risks incompatible with human rights standards).
- Accountability and responsibility for negative impact.

Official Journal
of the European Union

REGULATION (EU) 2024/1689 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 June 2024

laying down harmonised rules on artificial intelligence and amending Regulations (EC) No 300/2008, (EU) No 167/2013, (EU) No 168/2013, (EU) 2018/858, (EU) 2018/1139 and (EU) 2019/2144 and Directives 2014/90/EU, (EU) 2016/797 and (EU) 2020/1828 (Artificial Intelligence Act)

Intersections

- MDR (2017)
- EHDS (2025)
- GDPR (2016)
- DGA (2021)
- Directive for Product Liability (2024)

11

Tech

Hard-fought provision on the AI Act could become obsolete, experts say

A key provision in the EU's AI rulebook to assess the risks of foundation models such as ChatGPT may become obsolete withi a year due to the pace of developing technologies, experts told Euractiv.

Code of Best Practices on Generative AI, approved within the US-EU Trade and Technology Council.

12

Some slits….

AIA does not apply to (art. 2):

- **R&D AI**: AI systems specifically developed for the sole purpose of **scientific R&D**
- **Domestic AI:** AI systems used by natural persons in the course of a purely personal non-professional activity.

13

Entry into force

AIA Act entered into force on **1 August 2024**.
Fully applicable 2 years later on **2 August 2026**, with some EXCEPTIONS:

- **prohibitions and AI literacy obligations** entered into application from 2 February 2025
- **governance rules and obligations for general-purpose AI models** will become applicable on 2 August 2025
- **rules for high-risk AI systems** - embedded into regulated products - have an extended transition period until 2 August 2027

14

European Parliament
2014-2019

TEXTS ADOPTED

P8_TA(2017)0076

Fundamental rights implications of big data

European Parliament resolution of 14 March 2017 on fundamental rights implications of big data: privacy, data protection, non-discrimination, security and law-enforcement (2016/2225(INI))

15

1.- Discrimination

- EU- Agency for FR outlines the potential discrimination in using AI for making decisions

- It also suggests potential ways for **minimizing risk of discrimination.**
  - Explaining how algorithms were built in order to rectify discriminatory applications.
  - Assessing the impact of potential biases resulting from algorithms.
  - Assessing the quality of data collected.

16

- **2.- Lack of security-** In need of organizational and security measures

- **3.- Lack of accuracy**: Predictive analysis based on AI sometimes can only offer a **statistical probability**.

Casuality vs Causality

Spurious Correlations

(European Parliament, 2017)

17

Loss of control over AI systems

The European Parliament has proposed the inclusion of a so-called '**kill switch' on all robots**

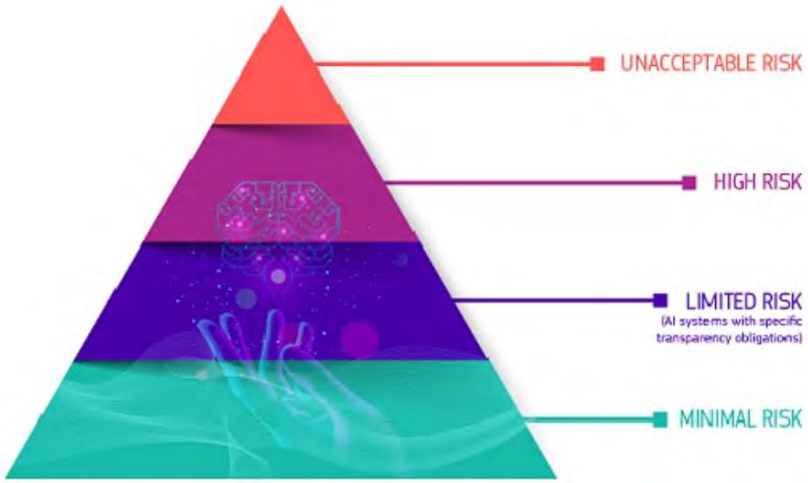
It would allow them to be deactivated

if they threaten the life of a human being.

18

A risk-based approach

The AI Act defines 4 levels of risk for AI systems:



19

Type of High-Risk AI system for health purposes	Regulation	Prior checking mechanism
AI systems – medical devices	Art. 6(1) AI Act Annex I	**Conformity Assessment (MDR)**
AI systems – non medical devices • Triage system in • emergency healthcare • Life insurance • Access to healthcare benefits	Art. 6(2) AI Act Annex III	**Fundamental rights impact assessment** Which deployers? • bodies governed by public law • private entities providing public services

20

1. Psychiatric ChatBot-based in GenAI

Mental health chatbots powered by artificial intelligence developed as a therapy support tool

Woebot Health founder Alison Darcy

60 MINUTES

Woebot is an app on your phone... kind of a pocket therapist that uses the text function to help manage problems like depression, anxiety, addiction, and loneliness... and do it on the run.

2. AI system for predicting cancer patients' response to immunotherapy

NIH RESEARCH MATTERS

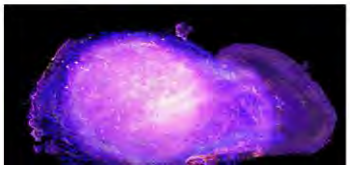
June 25, 2024

AI tool predicts response to cancer therapy

At a Glance

- Scientists developed an AI tool that uses routine clinical data to identify cancer patients most likely to respond to immunotherapy drugs called checkpoint inhibitors.
- The approach could help guide personalized cancer treatments for patients.

Chemotherapy, radiation, and surgical removal of tumors have long been the standard approaches for treating different types of cancer. But in recent decades, different immunotherapies have become available. These rely on the body's immune system to find and destroy cancer cells. One type of immunotherapy, called checkpoint inhibition, has greatly improved the treatment of many types of cancer. Immune checkpoint inhibiting drugs can make cancer cells more vulnerable to immune system attack. But they don't work for everyone.



3. AI-assisted reading of mammograms

BREASTCANCER•ORG Learn Connect About us

Research News

AI-Supported Mammogram Reading Detects 20% More Cancers

Using artificial intelligence to help read mammograms found more cancers than the standard double reading by two radiologists.

1. AI system for emergency call classification

PLOS Digit Health. 2023 Dec; 2(12): e0000406.
Published online 2023 Dec 6. doi: 10.1371/journal.pdig.0000406
PMCID: PMC10699611
PMID: 38055710

AI-based approach for transcribing and classifying unstructured emergency call data: A methodological proposal

Emergency care-sensitive conditions (ECSCs) require rapid identification and treatment and are responsible for over half of all deaths worldwide. Prehospital emergency care (PEC) can provide rapid treatment and access to definitive care for many ECSCs and can reduce mortality in several different settings. The objective of this study is to propose a method for using artificial intelligence (AI) and machine learning (ML) to transcribe audio, extract, and classify unstructured emergency call data in the Serviço de Atendimento Móvel de Urgência (SAMU) system in southern Brazil. The study used all "1-9-2" calls received in 2019 by the SAMU Novo Norte Emergency Regulation Center (ERC) call center in Maringá, in the Brazilian state of Paraná. The calls were processed through a pipeline using machine learning algorithms, including Automatic Speech Recognition (ASR) models for transcription of audio calls in Portuguese, and a Natural Language Understanding (NLU) classification model. The pipeline was trained and validated using a dataset of labeled calls, which were manually classified by medical students using LabelStudio. The results showed that the AI model was able to accurately transcribe the audio with a Word Error Rate of 42.12% using Wav2Vec 2.0 for ASR transcription of audio calls in Portuguese. Additionally, the NLU classification model had an accuracy of 73.9% in classifying the calls into different categories in a validation subset. The study found that using AI to categorize emergency calls in low- and middle-income countries is

2. AI systems for patient triage in the emergency department

Telefónica

4.24 EUR +0.03 (+0.59%) ES | EN

ABOUT US | SUSTAINABILITY AND INNOVATION | SERVICES | COMMUNICATION ROOM | SHAREHOLDERS AND INVESTORS | TALENT

HOME / COMMUNICATION ROOM / PRESS ROOM / TELEFÓNICA TECH AND 3M OPTIMISE HOSPITAL EMERGENCIES WITH AI

Telefónica Tech and 3M optimise hospital emergencies with AI

Telefónica Tech and 3M are launching in the Spanish market a pioneering technological solution with predictive capabilities, based on Artificial Intelligence, aimed at optimising the management and planning of Hospital Emergency Department (HED) resources and improving patient satisfaction.

The solution, which combines the technological capabilities of Telefónica Tech and 3M, offers a comprehensive view of HED operations so that healthcare professionals can identify areas for improvement and speed up data-driven decision-making. On the one hand, it integrates key service indicators (activity, occupancy, pathologies and procedures, among others) into 3M's 'Visor 360' scorecard and, on the other, a module with advanced analytics that shows the prediction of daily ED visits a week in advance to improve waiting times and optimise the sizing of the service.

Sandboxes

- **Sandbox:** Regulatory test bed with regulatory exemption
- **Living lab:** co-creation processes involving different actors in an open ecosystem of innovation**.**

26

AI regulatory sandboxes

- **National level:** MS shall establish at least 1 AI regulatory sandbox

Deadline: 2 August 2026.

- **Regional or local level:** Additional AI regulatory sandboxes may be established (jointly with the competent authorities of other MS)
- **EU level:** The European Data Protection Supervisor may also establish an AI regulatory sandbox for Union institutions

27

(Some) concluding remarks

- Misregulation of AI Act regarding AI Systems in health care.
- AI Act outdated (GenAI)
- Missing intersections with other norms
- Gaps (right to explanation)

28

WELLBEING APPS: HEALTHCARE & NEW TRENDS FROM A REGULATORY VIEW

Workshop on new ELSI related to AI and data processing in the health care arena

5&6 March 2025, Room 6B – Edificio Biblioteca Central / Main Library – Campus de Leioa (UPV/EHU)

Convenio para impulsar la Implementación de la Carta de Derechos Digitales en el Ámbito 5, de Entornos Específicos (ref C036/23-OT)

GODAS: Proyecto PID2022-137140OB-I00, financiado por el MCIN/AEI/10.13039/501100011033/FEDER, UE

1. REFERENCE TO THE CONCEPT OF DIGITAL HEALTH (E-HEALTH, BIG DATA AND M-HEALTH)

2. HEALTHCARE AND WELLBEING APPS

1. REFERENCE TO THE CONCEPT OF DIGITAL HEALTH (E-HEALTH, BIG DATA AND M-HEALTH)

E-HEALTH AT THE SERVICE OF HEALTH CARE

ELECTRONIC CLINICAL HISTORY
ELECTRONIC RECIPE
ROBOTIC SURGERY
NANOTECHNOLOGY AT THE SERVICE OF HEALTH
TELEMEDICINE
ONLINE MEDICATION
THE FULL INTEGRATION OF E-HEALTH: THE PAPERLESS HOSPITAL
MASSIVE DATA ANALYSIS: HEALTH BIG DATA
OUTSOURCING HEALTH DATA: DATA IN THE CLOUD
DATA PRIVACY IN ELECTRONIC HEALTH. CYBER ATTACKS
E-LEARNING (professionals and patients)
MOBILE HEALTH

E-HEALTH (electronic health): disruptive technological evolution/new forms of healthcare.

Telemedicine: Modern concept since1996 – California.

OMS 1997: “The practice of health care with the aid of interactive communications of sound, images and data; This includes the provision of medical care, consultation, diagnosis and treatment, as well as teaching and the transfer of medical data”.

UE 2008:Global system of computer and telematic communications (allows remote patient care = required health care through tools and services based on information and communications technologies from one's own home, or also receives early alerts that allow better and more precise diagnoses to be made – teleconsultation, telehealth, telecare,…).

AUTONOMY, LIABILITY AND HEALTH DATA PROTECTION

Patients' liability: The presence and use of connected objects will allow the patient to monitor their health status and adopt behavior consistent with their knowledge.

Liability of care providers: The digitalization of medical information on a large scale and the treatment using big data techniques will also lead to changes in the parameters for attributing liability when artificial intelligence tools are part of the state of science. are incorporated into the lex artis ad hoc.

EHR: Closely related to autonomy, the digital medical record offers the possibility of processing all patient information in order to coordinate care.

Health data: The processing of data derived from clinical documentation is a powerful tool for biohealth research.

Data protection related to health.

Pros

- Active patient: connectivity (autonomy and responsibility) / follow-up (monitoring of clinical parameters)
- Suggestion of activities on demand: exercise, rehabilitation
- Improved adherence to treatment
- Reduction of consultations on key issues (e.g. chronic follow-up)

Cons

- Correct use of data
- Replacement of personal consultations
- Scientific certainties/evidence

¿SPECIFIC REGULATION?

1. There is no specific regulation regarding the provision of healthcare at a distance.

2. The rules governing the professional practice of medicine must be observed:

➔ Basic principles of the doctor-patient relationship.

➔ Patients' rights to autonomy, information and confidentiality.

3. Law 44/2003, of 21 November, on the regulation of the health professions (Article 4.7): '*The exercise of the health professions shall be carried out with full technical and scientific autonomy, with no limitations other than those established by law and by the other principles and values contained in the legal and deontological system (...)'.*

BIG DATA (AI) GENERAL APPROACH

Context: New technologies, contemporary transformations and e-health.

- Treatment of large volumes of data for processing or reuse

- Purpose: Application of big data analysis in health, together with processes and tools based on artificial intelligence, the aim is basically to **increase the effectiveness and efficiency of medical diagnoses and clinical treatments**

- Scientific novelty: Not the data, but its origin (processes for collecting large amounts of data from different sources) + subsequent analysis (finding new correlations, patterns or 'hidden' information).

In healthcare, the use of ‘big data’ or ‘data intelligence’ translates into the **potential cross-referencing of multiple information**, be it family history, environment, lifestyle habits, medical records from a wide range of sources, etc (beware of data protection)!!!

Personalised medicine: Aims to determine personal predictive models for each patient, involving the early detection of many diseases.

M-HEALTH

- The new mobile devices have become an extension of our body and, for this reason, they are considered to be the best tool for keeping track of our medical, sports and dietary data...

- Advanced management of the information generated, diagnosis, treatment, or monitoring of diseases and health education

- **Mobile health (mHealth) is a part of e-health**, in which mobile health applications are used for self-assessment or to enable remote monitoring - Professional and patient interaction via mobile devices and applications.

- OMS: '*The practice of medicine and public health supported by mobile devices such as phones, patient monitoring devices, digital assistants and other wireless devices'*

Examples:

a) Lifestyle and wellness that connect people to medical devices or sensors,

b) Kidney failure patients can wear an artificial device that is remotely monitored by patients themselves via their smartphones and by healthcare staff,

c) Medication reminders,

d) Health information via messaging and telemedicine services.

2. HEALTHCARE AND WELLBEING APPS

NEW CONCEPTS

- Appscription: the doctor prescribes apps

- Appdemecum: a tool for prescribing ‘apps’ aimed at healthcare professionals

Typologies:

- Professionals (30%) vs. users/patients (70%)

- Clinics / medical (lead to clinical decision making, diagnosis or treatment as well as those powered by medical devices: evaluated)

- Well-being / 'healthy' life / sport: self-management of health without initially requiring the intervention of a health professional

- Disability support apps: e.g. text to speech (communication skills)

Purposes: Motivate, inform, raise awareness, cooperate in diagnosis or treatment - Chronic follow-up; improve patient autonomy (medication reminders); reduce unnecessary consultations; macro-data analysis,...

Subcategories: Well-being / ‘healthy’ life / sport

- **Information**: text, image or video format

- **Education and awareness**: empowering the patient (getting expert)

- **Recording and monitoring parameters**, except medical devices (-> medical)

- **Reminder and follow-up of treatments:** supporting patients to improve their adherence to treatments

- **Administrative procedures and other utilities**

2021: + 350.000

(90.000 solo en 2020)

Economic value: $50 billion (2030: +$800 billion)

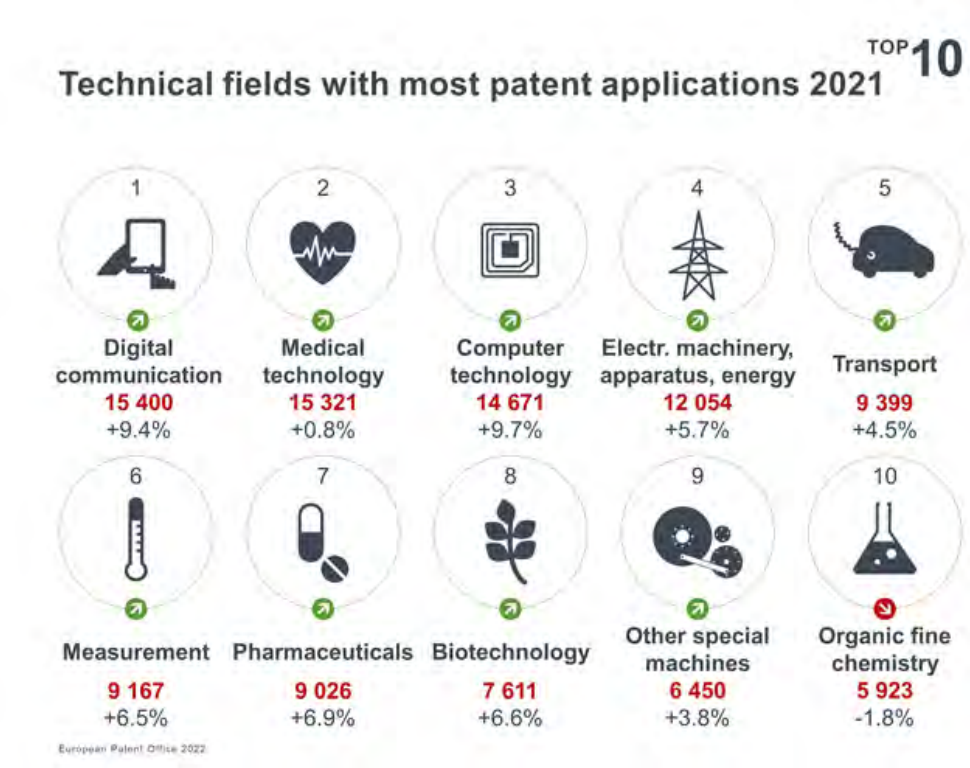
Allied Market Research (AMR) forecasts that by 2030 the global **fitness apps market** will reach USD 120.37 billion, or EUR 111.47 billion.

Opportunities for expansion are expected from *'technological advances in artificial intelligence, machine learning and the rising prevalence of diseases such as hypertension*'.

HEALTH TECHNOLOGIES AND PATENTS

The need for new equipment for services drives a market estimated at €450 billion (end 2019).

In 2017, the European Patent Office registered +13,000 new medical technology products, more than those related to digital communications (from stethoscopes, to MRI devices).




SCS


SCS
Hola Yolanda
Inicio
Mis Citas
Mis Datos De Salud
Datos de Contacto Tarjeta Sanitaria
Tarjeta Sanitaria Virtual
Resultados de laboratorio
Mis Informes Clínicos
Receta Electrónica


¿Estás pensando en hacer una App de salud?
GooApps
Aprovecha nuestros 10 años de experiencia para hacer productos innovadores centrados en las personas
CONTACTAR
PRESASURE


aemps
cima

Medicat-e: The Hospital Mare de Déu de la Mercè in Barcelona, creator of an 'app'.

Improving adherence to medication for psychiatric patients

Professional can know at all times if they are following the treatment, which reduces the risk of relapse in the disease

31 julio, 2019

Medicat-e

Published on 25.4.2022 in Vol 24 , No 4 (2022) :April

Preprints (earlier versions) of this paper are available at https://preprints.jmir.org/preprint/29088, first published May 20, 2021.

Effectiveness of Web-Based Personalized Nutrition Advice for Adults Using the eNutri Web App: Evidence From the EatWellUK Randomized Controlled Trial

Rodrigo Zenun Franco [1]; Rosalind Fallaize [2,3]; Michelle Weech [2]; Faustina Hwang [1]; Julie A Lovegrove [2]

Abstract

Background:
Evidence suggests that eating behaviors and adherence to dietary guidelines can be improved using nutrition-related apps. Apps delivering personalized nutrition (PN) advice to users can provide individual support at scale with relatively low cost.

Objective:
This study aims to investigate the effectiveness of a mobile web app (eNutri) that delivers automated PN advice for improving diet quality, relative to general population food-based dietary guidelines.

Methods:
Nondiseased UK adults (aged >18 years) were randomized to PN advice or control advice (population-based healthy eating guidelines) in a 12-week controlled, parallel, single-blinded dietary intervention, which was delivered on the web. Dietary intake was assessed using the eNutri Food Frequency Questionnaire (FFQ). An 11-item US modified Alternative Healthy Eating Index (m-AHEI), which aligned with UK dietary and nutritional recommendations, was used to derive the automated PN advice. The primary outcome was a change in diet quality (m-AHEI) at 12 weeks. Participant surveys evaluated the PN report (week 12) and longer-term impact of the PN advice (mean 5.9, SD 0.65 months, after completion of the study).

Results:

Citation

Please cite as:

Zenun Franco R, Fallaize R, Weech M, Hwang F, Lovegrove JA
Effectiveness of Web-Based Personalized Nutrition Advice for Adults Using the eNutri Web App: Evidence From the EatWellUK Randomized Controlled Trial
J Med Internet Res 2022;24(4):e29088
doi: 10.2196/29088
PMID: 35468093
PMCID: 9154737

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This paper is in the following e-collection/theme issue:

Innovations and Technology for Healthy Eating Education (312)

Obesity and Nutrition as Public Health Problem (167)

Obesity (48)

Prevention and Health Promotion (403)

Mobile Health (mhealth) (1863)

Public Health (79)

Web-based and Mobile Health Interventions (2053)


DEPRESSION
elona
Depression (€535,49) – new trial period 12/26/22-12/25/23
edu
Depression (€357,00 1st Rx, €178,50 follow up Rx) – new trial period 12/26/22-8/25/23
novego
Depression (€297,50)
Selfapy
Depression (€217,18) - €182,50 NET price, Dec22 reported retroactive price change
deprexis GAIA
Depression (€210,00)
MSK DISORDERS
medi Companion patella
Musculoskeletal (€345,10)
MAWENDO
Musculoskeletal disease of the kneecap (€119,00)
reflex
Gonarthrosis, knee (€784,21)
VIVIRA
Back, Knee & Hip Pain – 40 indications (€211,72) – 1/1/23 price change
PANIC DISORDERS
Agoraphobia, Panic Disorder and Social Phobias (€620,00)
invirto
Panic Disorder and Agoraphobia (€576,00)
Mindable
Panic Disorder (€599,00)
HelloBetter
Agoraphobia, Panic Disorder, GAD, Social Phobias (€230,00)
velibra GAIA
DIABETES
Diabetes + Depression (€222,99) – 12/11/22 price change
HelloBetter
Diabetes (€499,80)
vitadio
SUBSTANCE USE DISORDERS
Tobacco Addiction, Smoking Cessation (€329,00 1st Rx, €119,00 follow up Rx)
Hero app
Alcohol Dependence (€192,01)
VORVIDA GAIA
STRESS & ANXIETY
Selfapy
GAD (€479,52)
HelloBetter
Burn Out and Stress (€235,00)
INSOMNIA
HelloBetter
Organic & Non-organic Insomnia (€599,00)
somnio
Inorganic insomnia (€224.99)
40 DiGAs
Reimbursed in Germany
DiGA Listing Color Key: Permanent (BLACK), Provisional (RED)
Price Shown: Gross Price (negotiated, arbitrated, or not)
BREAST CANCER
Breast Cancer survivors (€952,00)
optimune GAIA
Breast Cancer (€535,50)
PINK!
Breast Cancer (€399.84)
CANKADO
OBESITY
Obesity in Women (€499,80)
zanadio
Obesity (€426,96)
OVIVA
TINNITUS
My Tinnitus App
Tinnitus (€449,00)
kalmeda
Tinnitus (€189,00)
3
EATING DISORDERS
4
Selfapy
Binge Eating Disorder (€540,00) – new trial period 1/5/23-5/4/23
Bulimia Nervosa (€540,00) – new trial period 1/5/23-5/4/23
Selfapy
GI DISORDERS
Irritable Bowel Syndrome (€718,20) - trial extension for 11 months to 11/25/23
caracare
9
7
8
WOMENS MENS HEALTH
HelloBetter
Vaginismus (€599,00)
Erectile Dysfunction (€856,88) - trial extension for 4 months to 4/17/23
endo app
Endometriosis (€598,95)
HelloBetter ratiopharm
Chronic Pain (€599,00) - trial extension for 7 months to 7/17/23
Cephalea
Migraine (€690,00)
10
OTHER INDICATIONS
5
COPD (€415,00) – new trial period 12/26/22-12/25/23
Aphasia and Dysphasia (€487,90)
kaia
Chiesi
MULTIPLE SCLEROSIS
Multiple Sclerosis (€2077,40) - new trial period 1/7/23-1/6/24
levidex GAIA
6
Multiple Sclerosis w/ fatigue (€243,00)
elevida GAIA
DiGA Directory De-Listings: 1) Mika for cancers (1/25/22), 2) M-sense for migraine (4/4/22), 3) Rehappy for post stroke care (9/26/22), 4) Esysta for T1/T2 diabetes (10/4/22), 5) Selfapy for Panic Disorder (11/16/22)
PalmHealthCo
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GERMANY (since 2020):

The integration of **digital health apps into the public health system** was seen as a significant innovation and many looked to Germany with interest and expectation. A few months later, a number of articles were published, in which the first experiences were generally assessed as positive,

Especially by doctors and psychotherapists, who saw the possibility of **patient empowerment** through digital health apps as a potential advantage.

Survey: 87% of doctors knew that they could prescribe DiGA, but only 22% trusted themselves to competently advise patients about apps (key: learning digital health).

According to some analyses the **average prices of apps** per user and 90 days of treatment would be between approximately €400 and €500.

EVALUATION AND ACCREDITATION OF MOBILE APPLICATIONS

INTERNATIONAL INITIATIVES

iMedicalApps; The Healthy Living Apps; Ranked. Curated Health Apps and Devices; NHS Apps Library; Myhealthapps.net; ORCHA; AppScript.

European Directory of Health Apps (helping patients self-management health).

NATIONAL INITIATIVES

Appsaludable; AppSalut; Appteca.

SUPERVISORY AUTHORITIES
(not only guidelines and recommendations)

- **FDA (USA):** Provides non-binding recommendations (Guidance) for new health apps, in addition to exercising control over those considered as **medical devices (sanctions if there is harm)**

- **AEPD** (network studies: Global Privacy Enforcement Network (GPEN) or the former Article 29 Working Group)

  Recommendations 2019 (Proactive Liability Technical Note): aimed at entities involved in the development/distribution/exploitation of health apps + those responsible for treatment (in general, actors in the 'app ecosystem').

  App Radar COVID

LEGAL REGIME FOR APPS

-> Applicable to computer programs (arts. 95 et seq. Intelectual Prop. Law)

-> Depending on the type of app, it may be considered as an information society service: '*any service normally provided for consideration, at a distance, by electronic means and at the individual request of the recipient'* (Law 34/2002, of 11 July, on information society services and electronic commerce)

-> Regulation of **medical devices** (AEMPS surveillance): **ALL APPS**?

-> <u>Advertising of medicinal products for human use</u>

Copyright and licence of use

Trademark

App licence agreement for users/buyers

Consumers and users

Protection of personal data of a personal nature

- Personal data: depending on where the respective app is hosted, i.e. on own or third-party servers (cloud) -> data processor + international data transfer.

- Types of data: provided by the professional, the user/patient, sensors and raw devices.

PARADIGM CHANGE

Patient care in rural areas, merchant navy or army missions (allows access to medical consultations when circumstances make travel difficult or dispensable).

Urgent and catastrophic situations: Support in decision-making.

Increasing use in health care which, although it could be carried out in person, it is considered more convenient or efficient to do so telematically.

Helping to better control and care for one's own health.

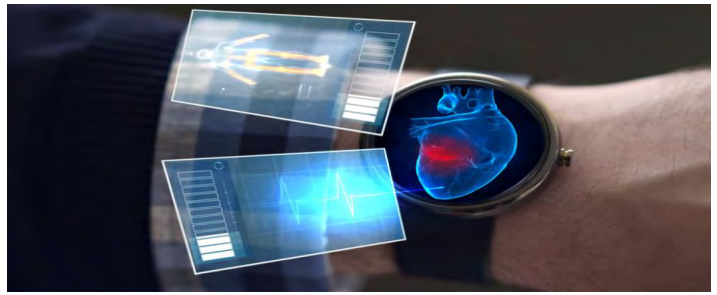
Patients: Minority of age -with or without maturity-, as well as in the case of patients with neurodegenerative pathologies or with altered cognitive capacities.

Is the **active patient ready** to access information, understand it and apply it to their decision-making?

In which cases can we affirm that the **digital patient is free** and that his or her decisions are the result of a conscious and responsible will?

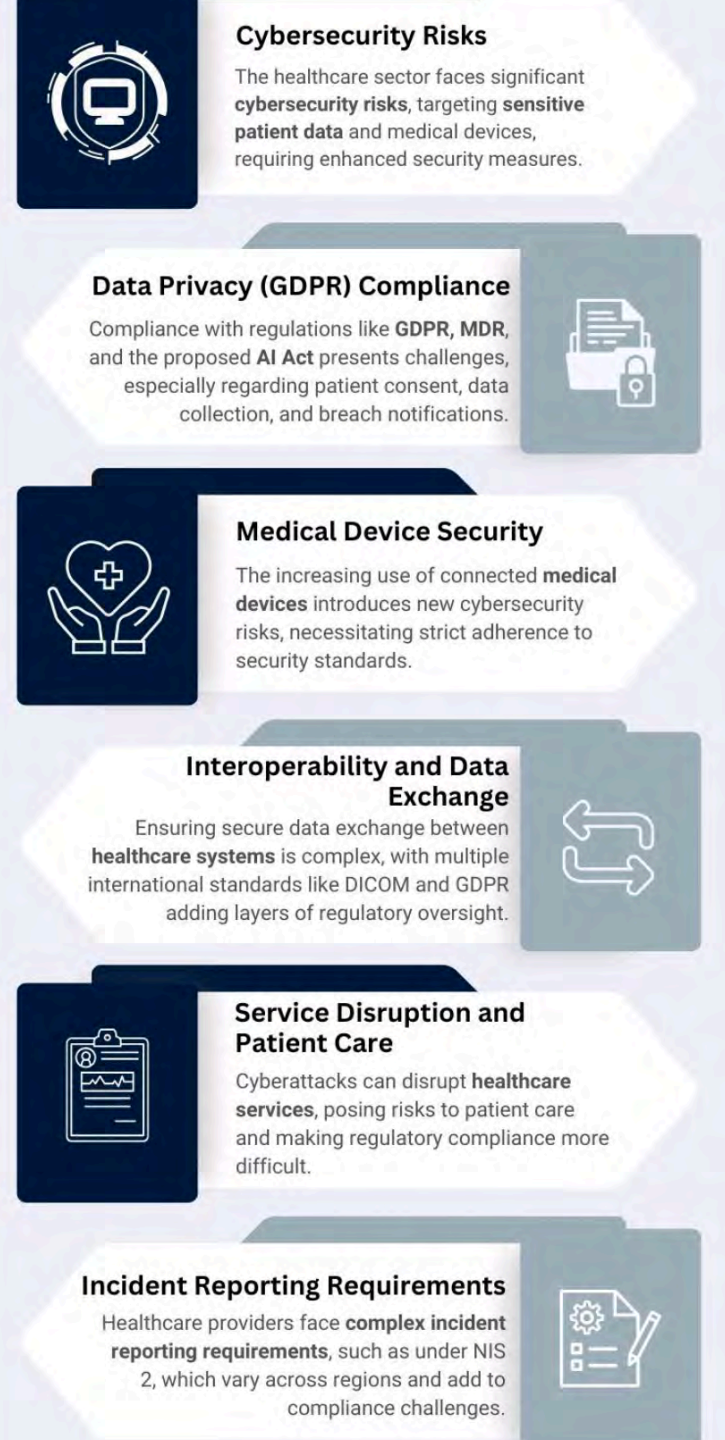
REASONABLE DOUBTS AND ASSOCIATED RISKS M-HEALTH

- Is it possible to ensure that health apps do their job and are reliable?
- As they work on the basis of algorithms, how can we know and certify whether they can be beneficial to our health?
- Is it possible to determine common key aspects for the regulation of these health apps?
- Do they comply with legal requirements on the confidentiality of our personal health-related data?
- Can all health apps be considered health products?



RECAP – KEY REGULATORY CHALLENGES

- ➔ Electronic procedures
- ➔ Electronic identity (locations, identification, processing and accreditation)
- ➔ Electronic data registers
- ➔ Biometrics and data protection -> Cloud and e-security
- ➔ Complex decision-making capabilities
- ➔ Remote healthcare (5G,...)



➔ Criteria for assessing apps - Medical device or not

➔ Consent, security and purpose of data processing

➔ Liability arising from the use of apps

➔ Ethical considerations.

LIABILITY (arising from the use of apps)

- Inherent complexity of imputation (several actors involved)
- Damage from different sources

*Examples according to origin of liability: software (Therac 25); manufacturer and AEMPS (Ala Octa)

Typology

- Medical professional (professional practice supported by a health app: depending on whether or not the doctor is involved in design and other aspects of the app)

- By defective product:
a) Manufacture
b) Design
c) Instructions and warnings

Mylife App is an application for recording diabetes therapy data and calculating insulin bolus for administration. In addition, it allows data to be read out with connected devices.

Example ‘SOFTWARE FAILURE’

AEMPS reports a failure in the application ’mylife App’

Reference: PS 43/2024 - Date of publication: 30 October 2024

Category: medical devices, safety.

-> AEMPS reports the possibility that, under certain circumstances, an insulin bolus delivered may not be permanently saved in the app's logbook when synchronising the app with the mylife Cloud at the same time

-> An error in the recording of an insulin bolus may lead to incorrect calculation and dosing of subsequent boluses.

Official Journal
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2025/327

5.3.2025

REGULATION (EU) 2025/327 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 11 February 2025

on the European Health Data Space and amending Directive 2011/24/EU and Regulation (EU) 2024/2847

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Articles 16 and 114 thereof,

- Definitions & relevance
- Right to be informed (users)
- Transparency, labelling & interoperability

REGULATION (EU) 2025/327 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 February 2025 on the European Health Data Space and amending Directive 2011/24/EU and Regulation (EU) 2024/2847 (05/03/2025)

Art. 1.2: This Regulation lays down common rules for…**wellness applications which are claimed to be interoperable with EHR systems**

Art. 2: ‘**wellness application**’ means any software, or any combination of hardware and software, intended by the manufacturer to be used by a natural person, for the processing of electronic health data, specifically for providing information on the health of natural persons, or the delivery of care for purposes other than the provision of healthcare.

Users of wellness applications, including applications for mobile devices, **should be informed** of the ability of such applications to connect and provide data to EHR systems or national e-health solutions, where the data produced by the wellness applications are useful for healthcare.

Users should **also be informed** about the compliance of such wellness applications with interoperability and security requirements.

-> However, given the large number of wellness applications and the limited relevance for healthcare purposes of the data produced by many of them, a **certification scheme for these applications would not be proportionate.**

A mandatory labelling scheme for wellness applications for which interoperability with EHR systems is claimed should therefore be established as an appropriate mechanism for providing transparency for the users of wellness applications regarding compliance with requirements under this Regulation, thereby supporting users in their **choice of appropriate wellness applications with high standards of interoperability and security.**

-> The Commission should set out by means of implementing acts the details regarding the format and content of such label.

Legal persons developing wellness applications should also be considered health **data holders**.

In order to ensure uniform conditions for the implementation of this Regulation, implementing powers should be conferred on the Commission as regards: (…) - format and content of the **label of wellness applications**

Article 47 Labelling of wellness applications

Where a manufacturer of a wellness application claims interoperability with an EHR system in relation to the harmonised software components of EHR systems and therefore compliance with the **common specifications referred to in Article 36 and essential requirements laid down in Annex II**, such wellness application shall be accompanied by a label, clearly indicating its compliance with those specifications and requirements. That label shall be issued by the manufacturer of the wellness application.

Article 48 Interoperability of wellness applications with EHR systems

Manufacturers of wellness applications may claim interoperability with an EHR system, provided that the relevant common specifications and essential requirements referred to in Article 36 and Annex II, respectively, are met. In the event of such claim, those **manufacturers shall duly inform users of the interoperability of such wellness applications and the effects of such interoperability.**

*The interoperability of wellness applications with EHR systems shall not entail the automatic sharing of all or part of the health data from the wellness application with, or automatic transmission of all or part of such data to, the EHR system.

*The sharing or transmission of such data shall only possible if it is in accordance with Article 5 and after consent is given by the natural person concerned

*The natural person concerned is able to choose which categories of health data from the wellness application are to be inserted in the EHR system and the circumstances for the sharing or transmission of those categories of data.

A **database** of interoperable EHR systems and **wellness applications**, which do not fall within the scope of Regulations (EU) 2017/745 and (EU) 2024/1689, should therefore be established at Union level, similar to the European database on medical devices (Eudamed) established by Regulation (EU) 2017/745.

Objectives: to enhance overall transparency, to avoid multiple reporting requirements and to streamline and facilitate the flow of information.

Article 49 - EU database for **registration** of EHR systems and wellness applications:

The Commission shall establish and maintain a publicly available EU database

The categories of electronic health data that can be processed for **secondary use** should also include automatically generated data from medical devices and person-generated data, such as data from wellness applications.

Article 51 - Minimum categories of electronic health data for **secondary use**

Health data holders shall make the following categories of electronic health data available for secondary use (…)

(i) data from wellness applications

QUESTIONS...

... THANK YOU VERY MUCH

The use of AI for developing medicines: regulatory landscape and challenges

Workshop on new ELSI related to AI and data processing in the health care arena

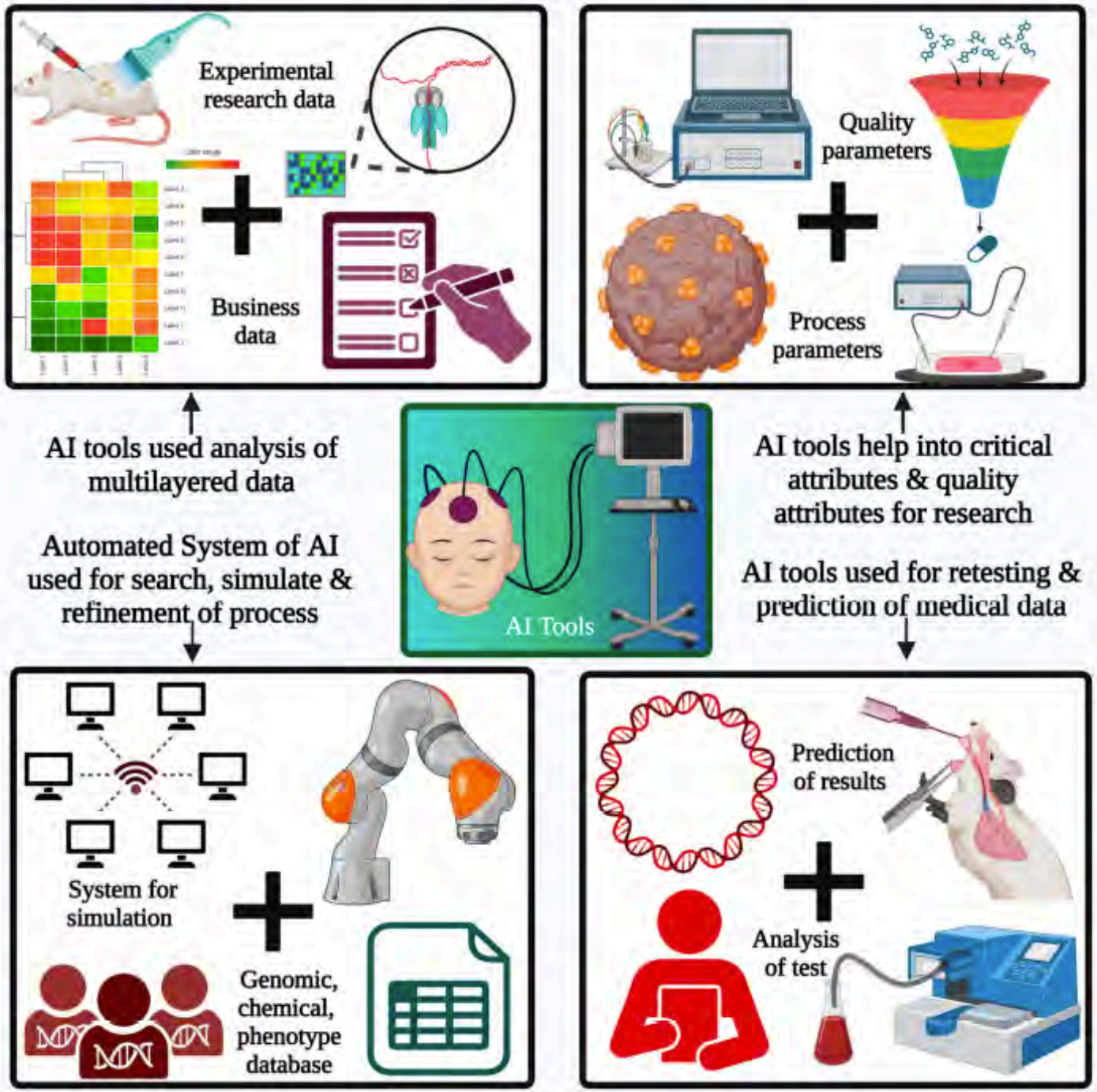
5&6 March 2025, Room 6B – Edificio Biblioteca Central / Main Library – Campus de Leioa (UPV/EHU)

Dr Anastasiya Kiseleva

Post-doc researcher

VUB, Belgium (LSTS and HALL research groups, Faculty of Law

VRIJE UNIVERSITEIT BRUSSEL



Vora, L.K.; Gholap, A.D.; Jetha, K.; Thakur, R.R.S.; Solanki, H.K.; Chavda, V.P. Artificial Intelligence in Pharmaceutical Technology and Drug Delivery Design. Pharmaceutics 2023, 15, 1916. https://doi.org/10.3390/pharmaceutics15071916

David Baker

"for computational protein design"

© Nobel Prize Outreach. Photo: Clément Morin

Demis Hassabis

"for protein structure prediction"

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John Jumper

"for protein structure prediction"

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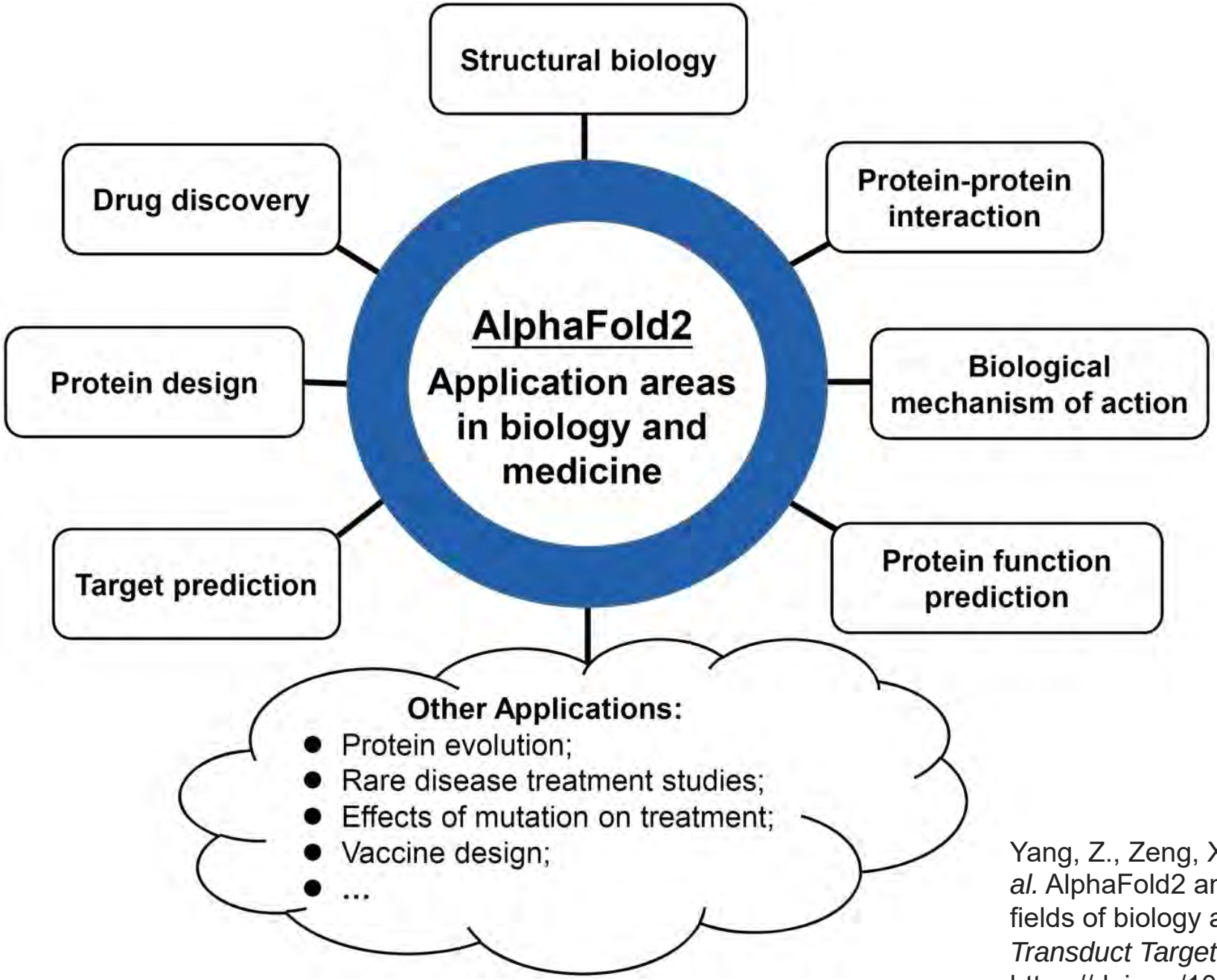
They cracked the code for proteins' amazing structures

The Nobel Prize in Chemistry 2024 is about proteins, life's ingenious chemical tools. David Baker has succeeded with the almost impossible feat of building entirely new kinds of proteins. Demis Hassabis and John Jumper have developed an AI model to solve a 50-year-old problem: predicting proteins' complex structures. These discoveries hold enormous potential.

Related articles

https://www.nobelprize.org/all-nobel-prizes-2024/



Yang, Z., Zeng, X., Zhao, Y. *et al.* AlphaFold2 and its applications in the fields of biology and medicine. *Sig Transduct Target Ther* **8**, 115 (2023). https://doi.org/10.1038/s41392-023-01381-z

EU Regulatory landscape for the use of AI in developing medicines

- **THE AI ACT: IS IT APPLICABLE?**
- The use of AI in developing medicines generally cannot qualify as high-risk AI applications as they are not covered by the Annex I and Annex III
- The AI Act exemption for AI dedicated to scientific research can apply (recital 25; art. 2.6 and 2.8)

EU Regulatory landscape for the use of AI in developing medicines

- **WHAT IS APPLICABLE THEN?**
- **Framework on Medicinal Products for Human Use** (Directive 2001/83/EC as of November 06, 2001, on the Community code relating to medicinal products for human use and the Regulation 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency)
- **Clinical Trials Regulation** (Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use)

EU Regulatory landscape for the use of AI in developing medicines

- **Is the applicable framework tailored to the unique nature of AI?**
- The authorisation of medicines builds on three key criteria, namely **quality, safety and efficacy**, to ensure that products administered to patients are of suitable quality and provide a positive benefit-risk balance.
- When applying for marketing authorisation, companies must provide **documentation** showing that the product is of suitable quality. For new medicines companies are required to demonstrate safety and efficacy through the results of clinical trials.
- The data on safety and efficacy will be carefully assessed by the competent authorities before a product receives marketing authorisation.
- Safety and efficacy continue to be monitored after marketing authorisation, through pharmacoviglance activities, or reviews of the benefit-risk balance.

EU Regulatory landscape for the use of AI in developing medicines

- **Is the applicable framework tailored to the unique nature of AI?**
- The applicable framework already provides quite a rigorous system of control and strict transparency obligations (clinical trials protocol);
- The EMA 2023-2028 workplan includes developing AI Guidance in Medicines Lifecycle (second half of 2024, delayed).

EU Regulatory landscape for the use of AI in developing medicines

- **EMA Reflection paper on the use of AI in the medicinal product lifecycle as of September 2024: AI in the lifecycle of medicinal products**
- Drug discovery; non-clinical development; clinical trials, data analysis and inference; precision medicine; product information; manufacturing; post-authorisation phase.

- The full model architecture, logs from model development, validation and testing, training data and description of the data processing pipeline would likely be considered parts of the clinical trial data or trial protocol dossier – clash with the IP rights and interests of pharma companies (EFPIA);

- When AI/ML models are used for transformation, analysis or interpretation of data within a clinical trial of a medicinal product, they are considered a part of the statistical analysis and should follow applicable guidelines on statistical principles for clinical trials.

EU Regulatory landscape for the use of AI in developing medicines

- **EMA Reflection paper on the use of AI in the medicinal product lifecycle as of September 2024: Regulatory interactions**
- Applicants and developers are expected to perform a regulatory impact and risk analysis of all AI/ ML applications and are recommended to seek regulatory interactions when no clearly applicable written guidance is available.

- Timing of interactions should be guided by the regulatory impact and risk associated with using the AI based models in context of the lifecycle of a medicinal product.

- The documentation to inform the interaction with regulators should cover questions such as intended context of use, generalisability, performance, robustness, transparency, and clinical applicability, at a level of detail sufficient for comprehensive assessment. Specific and clearly formulated regulatory and scientific questions are strongly encouraged, to allow reciprocally concise answers.

EU Regulatory landscape for the use of AI in developing medicines

- **EMA Reflection paper on the use of AI in the medicinal product lifecycle as of September 2024**
- **Technical aspects**: data acquisition and augmentation; training, validation, and test datasets; model development; performance assessment; interpretability and explainability; model deployment;
- **Governance**: documentation of processes and data;
- **Integrity aspects and data protection**;
- **Assessment List for Trustworthy Artificial Intelligence for self-assessment (ALTAI**): human agency and oversight; technical robustness and safety; privacy and data governance; transparency; accountability; societal and environmental well-being; diversity, non-discrimination, and fairness

Gene therapy

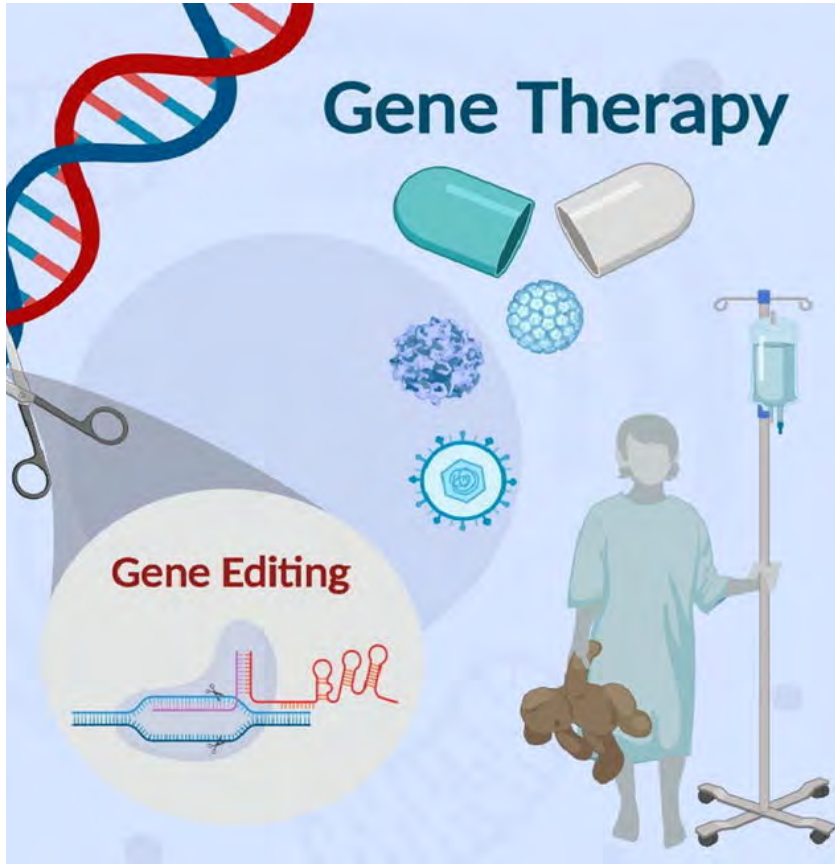
- Gene therapy is a technique that uses a gene(s) to treat, prevent or cure a disease or medical disorder. Both inherited genetic diseases (e.g., hemophilia and sickle cell disease) and acquired disorders (e.g., leukemia) have been treated with gene therapy (https://www.genome.gov/genetics-glossary/Gene-Therapy?id=77)
- In 1988, the first authorized human gene therapy clinical trial for the treatment of Gaucher disease signaled the dawn of human gene therapy (ClinicalTrials.gov identifier number: NCT00001234)
- Between 1988 and 2020: 2106 gene therapy clinical studies were reported and 16 products were placed on the market (with cancer as the leading disease)
- Types of gene therapy: in vivo (viral and non-viral vectors are used to deliver genetic material to target cells or tissues within a patient's body) and ex-vivo (removing targeted cells from the patient's body, separating and altering them, and reintroducing them into the body)

https://www.sciencedirect.com/science/article/pii/S1359644621001574

Gene editing and gene therapy

- Genome editing is one of the types of gene therapy (that might also include gene addition, gene silencing and cell elimination techniques)
- Genome editing is based on different technologies such as ZFN, TALEN and CRISPR/Cas9. These technologies act like scissors, cutting the DNA at a specific spot. Then scientists can remove, add, or replace the DNA where it was cut
- CRISPR, invented in 2009, has made it easier than ever to edit DNA. CRISPR is simpler, faster, cheaper, and more accurate than older genome editing methods
- In 2015, scientists successfully used somatic gene therapy when a one-year old in the United Kingdom named Layla received a gene editing treatment to help her fight leukemia, a type of cancer. This type of treatment is still at its experimental phase – risks are still not fully predictable

https://www.genome.gov/about-genomics/policy-issues/what-is-Genome-Editing
https://www.sciencedirect.com/science/article/pii/S1359644621001574



Regulatory framework for gene editing therapy

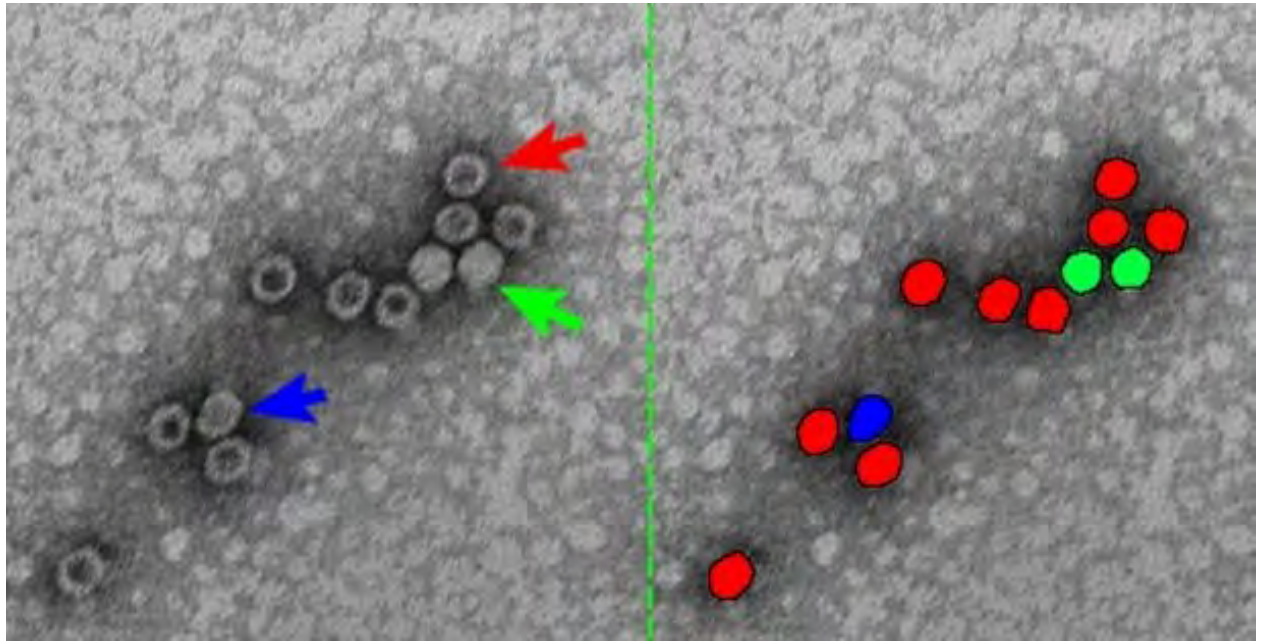
- Gene editing is the type of gene therapy medicinal products
- Gene therapy medicinal product is the type of advanced therapy medicinal product
- Advanced therapy medicinal products are covered by the Framework on Medicinal Products for Human Use, Clinical Trials Regulation and the ATMP Regulation (Regulation №1394/2007 as of 13 November 2007 on advanced therapy medicinal products)

AI in Somatic Genome Editing

- Identification of the harmful genes that shall be edited
- Accurate delivery of a new genetic code to a deceased cell
- Predicting and monitoring the consequences of genome editing

- Charles River developed AI-based algorithms that automatically assay digital **transmission electron microscopy** (TEM) images for the quality of genetic material packaged within viral capsids. **Capsids** are molecular structures that not only serve as a protective coating for the new code, but also help to facilitate its entry into a diseased cell.
- Not every capsid produced will contain the optimal gene construct, and the SGT will be compromised if too many empty capsids are present. Based upon the electron density of negatively stained preparations, trained AI determines whether a capsid contains the new genetic code (full capsid) or does not have the full code (partial or empty).

https://www.criver.com/insights/somatic-gene-therapy-cusp-major-innovation



Classification of viral capsids: empty (red); full (green); partially full (blue)

Applicable Legal Frameworks

Somatic Genome Editing =
Advanced Therapy Medicinal Products

- The ATMP Regulation
- Framework on Medicinal Products for Human Use
- Clinical Trials Regulation

AI medical applications =
Medical Devices

- EC Proposal for the AI Act
- Medical Devices Framework (Medical Devices Regulation (MDR) and In-Vitro Diagnosis Medical Devices Regulation (IVDR))

Classifications

AI-device is combined with an ATMP

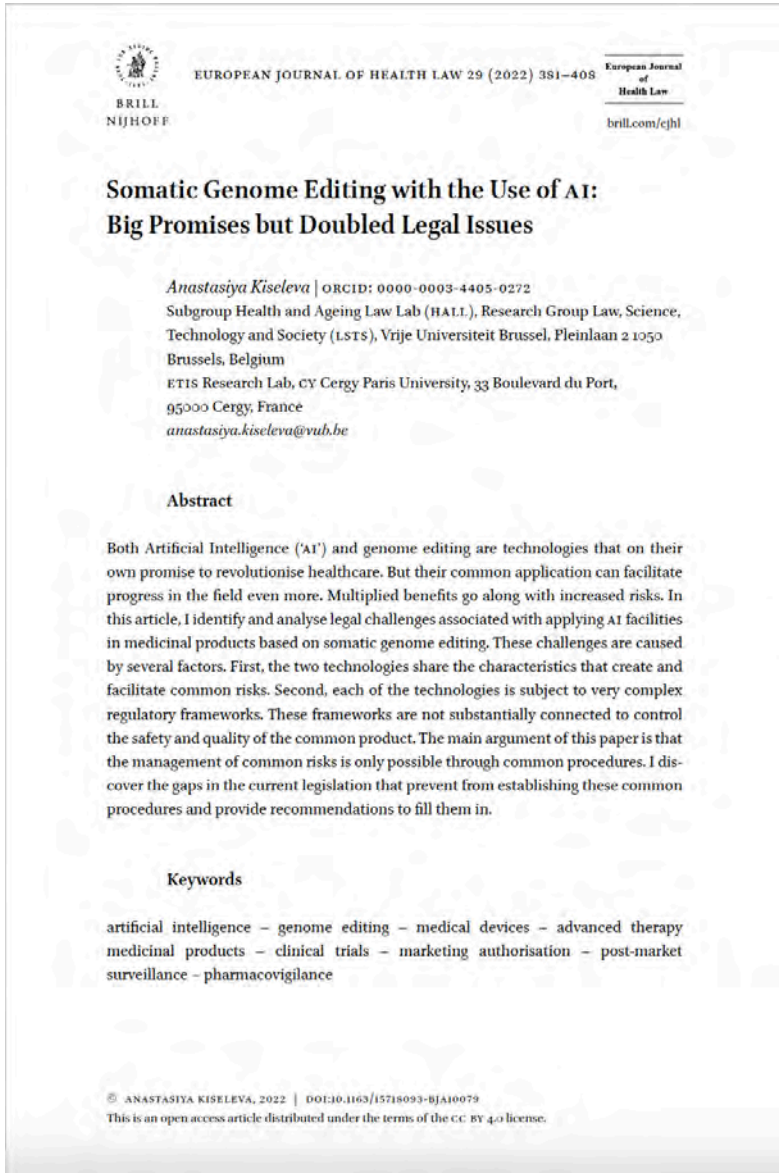
Accurate delivery of a new genetic code to a deceased cell

- AI-device is combined integrally with the ATMP
- MDR is applicable to the AI-element
- Constitutes the special type of ATMP – combined ATMPs (cATMPs)
- Authorised and controlled after placing on the market under the main framework: Framework on Medicinal Products for Human Use. The MA application shall include the results of the conformity assessment of the AI-device part

ATMP is companioned by AI-device

Diagnosis, identification of genes to be edited/ patients who are likely to benefit from treatment, prediction of consequences

- The ATMP can be used without the AI-part
- IVDR is applicable to the AI-element
- The ATMP and AI-device are verified , authorised and controlled after placing on the market separately
- When an AI-device is authorised, the notified body shall seek a scientific opinion from one of the competent authorities responsible for the ATMP to be companioned with the device



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Somatic Genome Editing with the Use of AI: Big Promises but Doubled Legal Issues

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Abstract

Both Artificial Intelligence ('AI') and genome editing are technologies that on their own promise to revolutionise healthcare. But their common application can facilitate progress in the field even more. Multiplied benefits go along with increased risks. In this article, I identify and analyse legal challenges associated with applying AI facilities in medicinal products based on somatic genome editing. These challenges are caused by several factors. First, the two technologies share the characteristics that create and facilitate common risks. Second, each of the technologies is subject to very complex regulatory frameworks. These frameworks are not substantially connected to control the safety and quality of the common product. The main argument of this paper is that the management of common risks is only possible through common procedures. I discover the gaps in the current legislation that prevent from establishing these common procedures and provide recommendations to fill them in.

Keywords

artificial intelligence – genome editing – medical devices – advanced therapy medicinal products – clinical trials – marketing authorisation – post-market surveillance – pharmacovigilance

https://brill.com/view/journals/ejhl/29/3-5/article-p381_4.xml

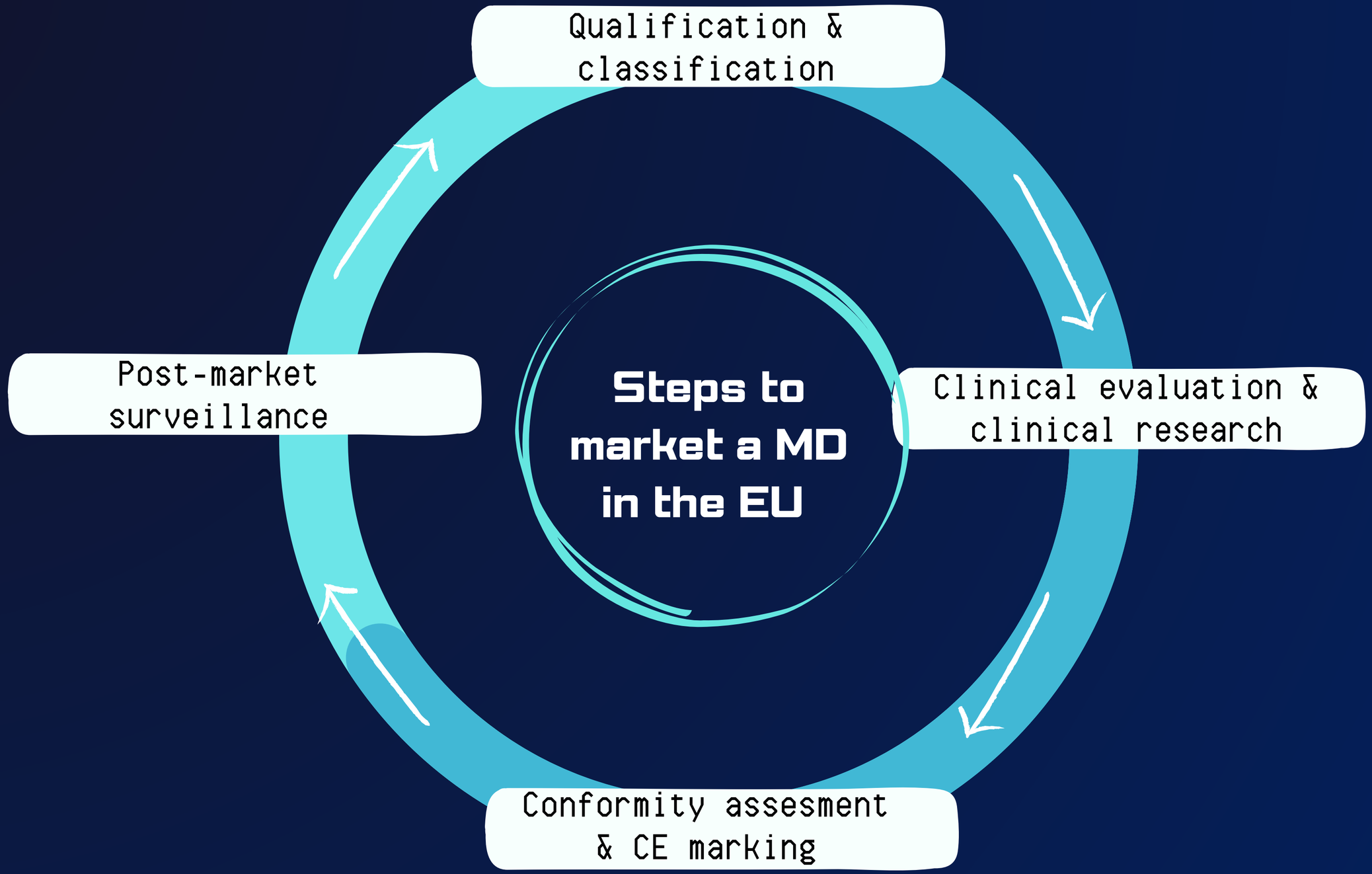
Thank you for your attention!

email me: anastasiya.kiseleva@vub.be

AI systems in biomedicine.

The long road to the markets

María Sánchez Besga


Qualification & classification
Clinical evaluation & clinical research
Conformity assesment & CE marking
Post-market surveillance
Steps to market a MD in the EU

MDR / IVMDR →

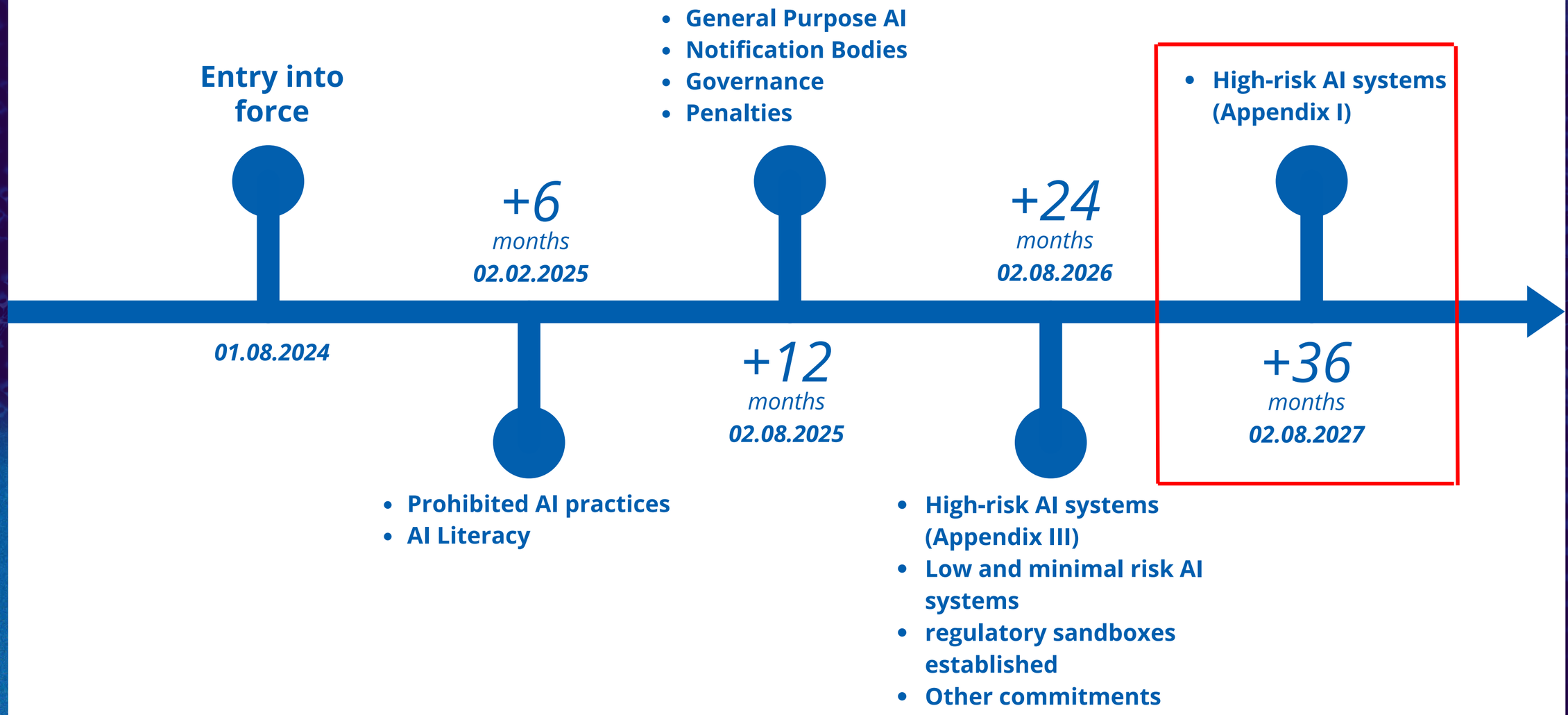
- SAFETY AND PERFORMANCE STANDARDS FOR MD
- PROTECTION OF USERS HEALTH

AI ACT →

- HORIZONTAL REGULATION
- SAFETY AND FUNDAMENTAL RIGHTS
- MOSTLY HIGH-RISK AI

AI Act: Time Frame

Overview of the most important provisions that will only gradually become valid



PRODUCT QUALIFICATION

Art. 2.1) MDR

any instrument, apparatus, appliance, **software**, implant, reagent, material or other article **intended by the manufacturer to be used,** alone or in combination, for human beings for one or more of the following **specific medical purposes**:

– diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of **disease**,
– diagnosis, monitoring, treatment, alleviation of, or compensation for, **an injury or disability**,
– investigation, replacement or modification of the **anatomy or of a physiological or pathological process or state**,
– providing information by means of in vitro examination of specimens derived from the **human body, including organ, blood and tissue donations**,

and which **does not achieve its principal intended action by pharmacological, immunological or metabolic means,** in or on the human body, but which may be assisted in its function by such means.

GUIDANCE ON QUALIFICATION OF SOFTWARE OCT. 2019

Medical Device Coordination Group

DOES THE PRODUCT MEET THE SOFTWARE DEFINITION?

a set of instructions that **processes** input data and **creates** output data.

INPUT DATA

OUTPUT DATA

IS THE SOFTWARE DOING MORE THAN STORAGE, ARCHIVAL, COMMUNICATION OR SIMPLE SEARCH OF INFORMATION?

THE ACTION IS PERFORMED FOR THE BENEFIT OF INDIVIDUAL PATIENTS?

CLASSIFICATION

Annex VIII MDR

- **Class I**

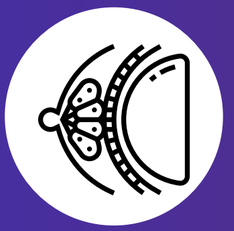
low risk

- **Class IIa**

medium-low risk

- **Class IIb**

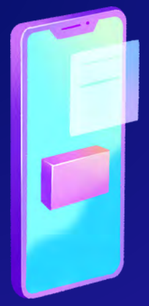
medium-high risk

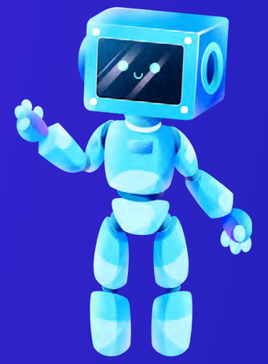


- **Class III**

high risk

According to
invasiveness and risk
to the patient's health



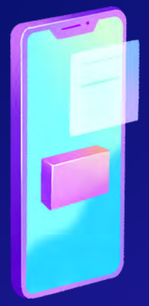


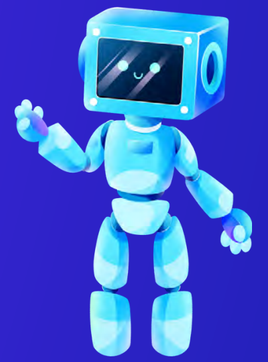


CLASSIFICATION OF SOFTWARE MD PRODUCT

Annex VIII Rule 11 MDR

Class I to Class III based on the impact of the *information* provided by the software on health.





"Software intended to provide information which is used to take decisions with diagnostic or therapeutic purposes is classified as **class IIa**, except if 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 in **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.**

Software intended to monitor physiological processes is classified as class IIa, except if 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.**

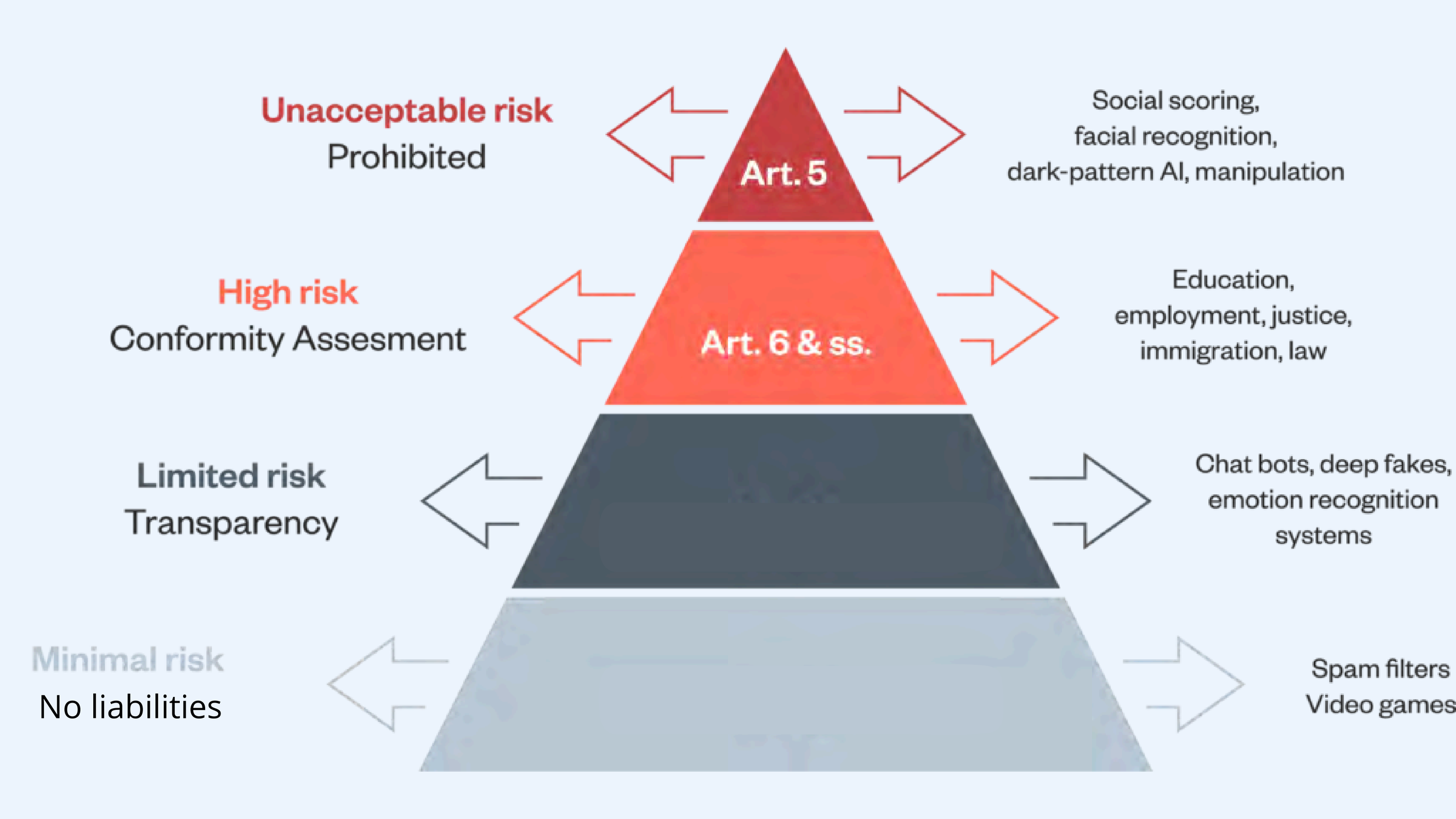
All other software is classified as **class I**".

Definition of AI system

Art. 3.1 AI ACT

a **machine**-based system that is designed to operate with varying levels of **autonomy** and that may exhibit adaptiveness after deployment, and that, for explicit or implicit objectives, **infers**, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that can influence physical or virtual environments;

- broad definition
- not applicable for AIS designed and used exclusively for scientific research purposes


Unacceptable risk
Prohibited
Art. 5
Social scoring,
facial recognition,
dark-pattern AI, manipulation
High risk
Conformity Assesment
Art. 6 & ss.
Education,
employment, justice,
immigration, law
Limited risk
Transparency
Chat bots, deep fakes,
emotion recognition
systems
Minimal risk
No liabilities
Spam filters
Video games

High risk AI

Art. 6.1 AI ACT

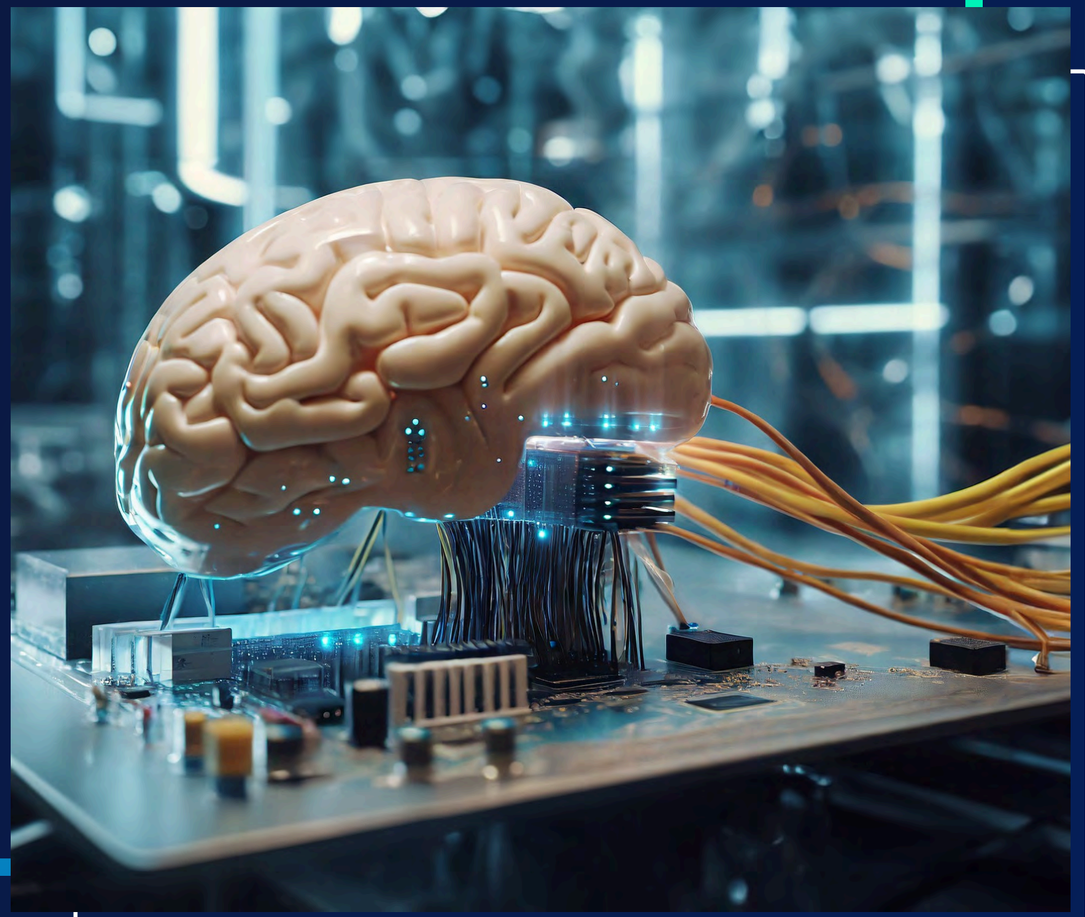
2 conditions:

- the AI system is intended to be used as a safety component of a product, or the AI system is itself a product, **covered by the Union harmonisation legislation listed in Annex I**;

AND

- the product whose safety component pursuant to point (a) is the AI system, or the AI system itself as a product, is required to **undergo a third-party conformity assessment,** with a view to the placing on the market or the putting into service of that product **pursuant to the Union harmonisation legislation listed in Annex I**.

Clinical evaluation and clinical research



Clinical **evaluation**:

Art. 61 and annex XIV A MDR

data analysis to verify the **safety, performance** and **benefit-risk acceptability** of the product

– mandatory for all MD

Clinical **research**:

Art. 61 to 82 MDR

systematic study involving human subjects, to verify the general **safety** and **performance** requirements defined in Annex I of the MDR

– new or innovative product

– lack of sufficient clinical data

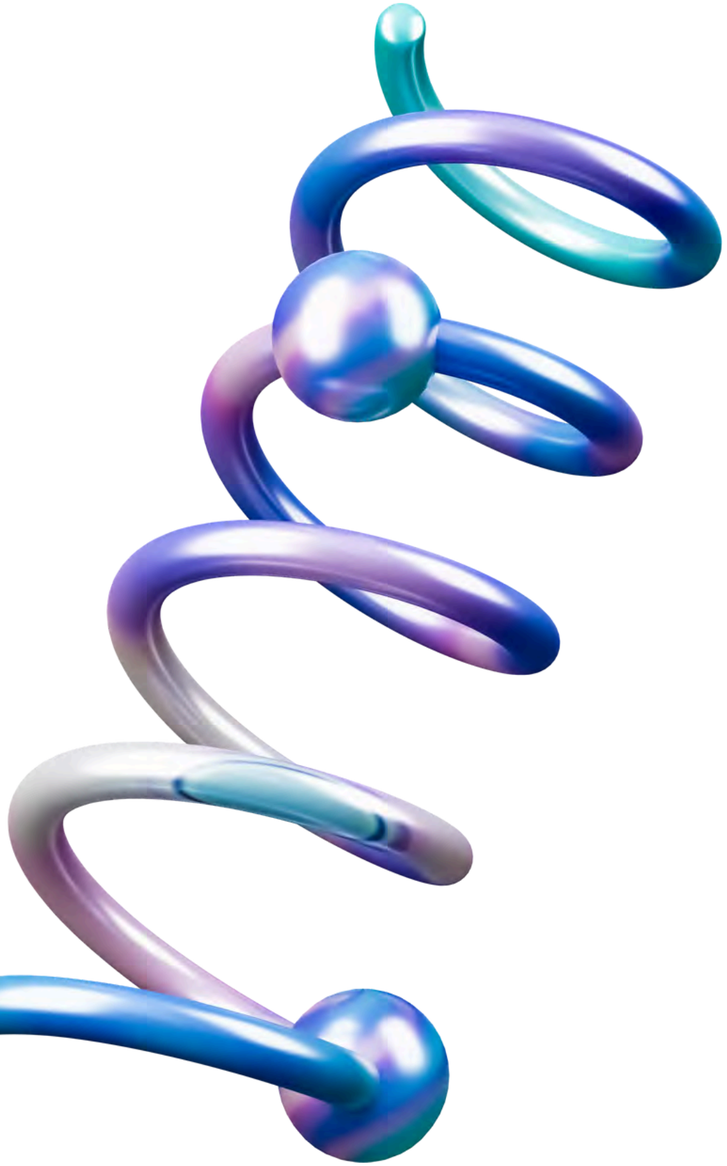
– high risk product (class III, implantable).

CONFORMITY ASSESMENT

- **Class I:** do not require the intervention of notified bodies except for *sterile*, with a *measuring function* or *reprocessed* MD
- **Class IIa:** Required
- **Class IIb:** Required
- **Class III:** Required

Even if an AI system is classified as high risk under the AI ACT, it does not necessarily mean that the MD is considered “high risk” under the criteria set out in the MDR.

Some AI software classified as class I MD under the MDR may be considered "high risk" under the AI ACT, requiring a notified body even though class I MD normally don’t.



COMMON REQUIREMENTS TO MDR AND AI ACT

- Quality management system
- Conformity assessment
- Technical documentation
- Risk management system
- Documentation and record keeping

- Appointment of an EU administrative representative
- Declaration of Conformity
- CE Marking
- Cooperation with the competent authorities

👉 Combinable procedures

Arts. 9 to 15 AI ACT

- Article 9: Risk Management System
- Article 10: Data and Data Governance
- Article 11: Technical Documentation
- Article 12: Record Keeping
- Article 13: Transparency and Communication of Information to Deployment Authorities
- Article 14: Human Oversight
- Article 15: Accuracy, Robustness, and Cybersecurity

Article 17 AI ACT

- Article 17: Quality Management System for the Measures in Articles 9 to 15.

Specific requirements for AI systems

Specific requirements for AI systems

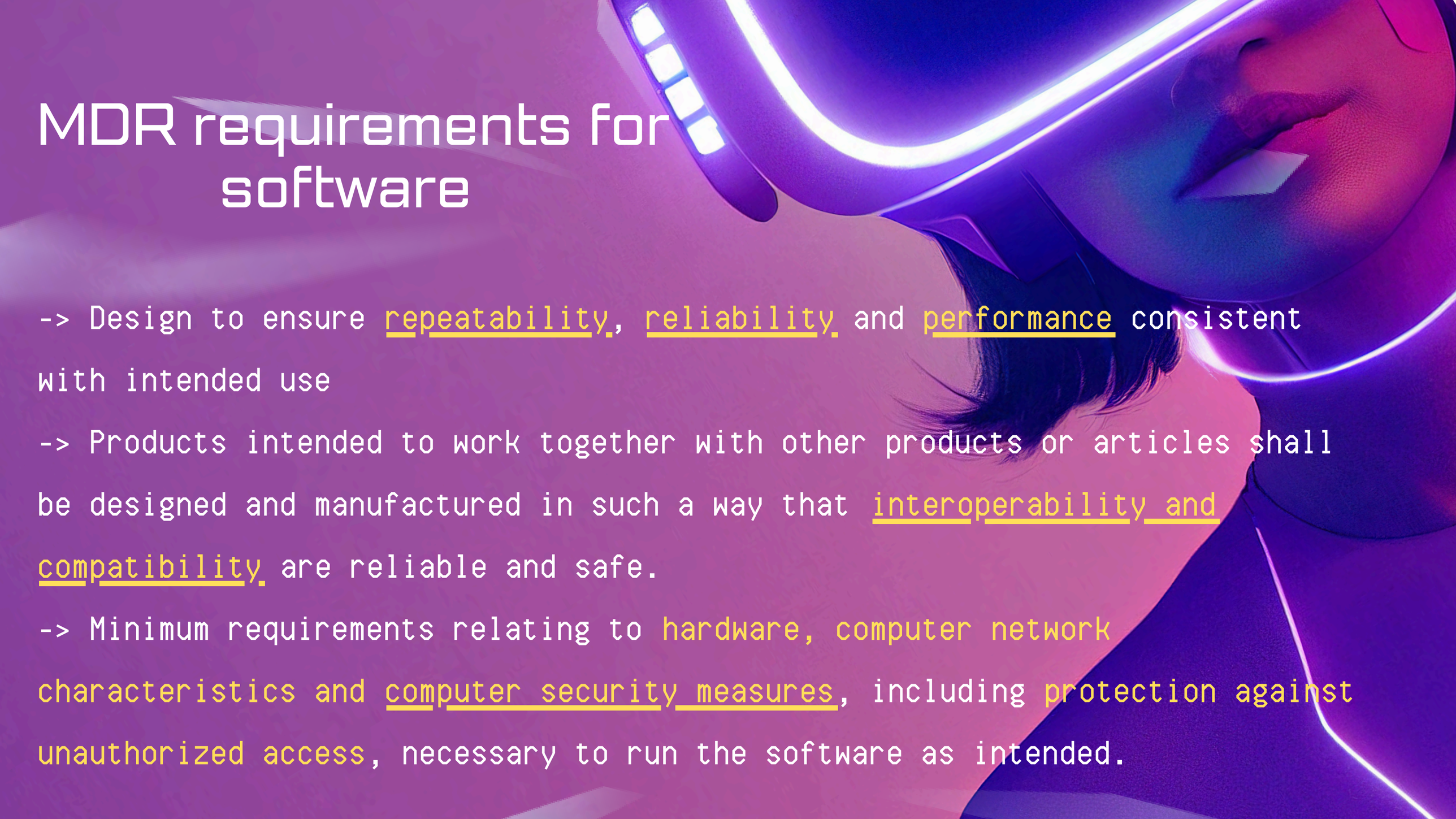
-> safety and cybersecurity standards

-> substantial modifications:

new conformity assessment if

- affects the compliance
- purpose of the AIS changes

MDR requirements for software



-> Design to ensure repeatability, reliability and performance consistent with intended use

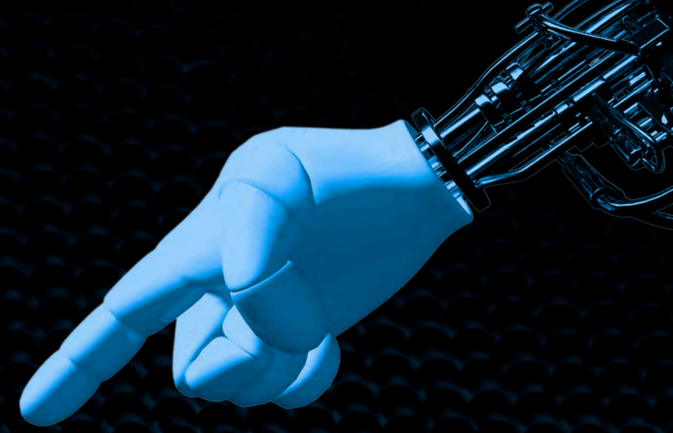
-> Products intended to work together with other products or articles shall be designed and manufactured in such a way that interoperability and compatibility are reliable and safe.

-> Minimum requirements relating to hardware, computer network characteristics and computer security measures, including protection against unauthorized access, necessary to run the software as intended.

CE marking

- **Allows the MD to be freely marketed and used throughout EU**
- **Commercialization: *"any supply of a device, other than an investigational device, for distribution, consumption or use on the Union market in the course of a commercial activity, whether in return for payment or free of charge"***
- **Notified body VS self-assessment of conformity**
- **The notified bodies designated under the MDR must also have specialized AI personnel and adequate facilities.**

POST-MARKETING SURVEILLANCE



Challenges

- Complex and intricate regulatory framework
- Anticipation: deep learning
- Substantial clinical evaluation and research: accuracy, reliability, safety and lack of discrimination


THANK YOU FOR YOUR
ATTENTION