The regulatory impact of a harmonized artificial intelligence regulation proposal on the clinical research landscape in the European Union

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ABSTRACT: This article offers a critical analysis of how the proposed Artificial Intelligence Act (AIA) will support the rights, safety, dignity, and well-being of clinical research participants and ensure the availability of reliable and robust data as described in Clinical Trials Regulation (EU) No. 536/2014. Analysis is focused on how the proposed regulation will impact clinical research conducted within the European Union. The proposed artificial intelligence regulation is evaluated based on what it will bring to the multiple stakeholders in clinical research – including sponsors, investigators, patients, society – and how it would align with the core principles of the Clinical Trials Regulation.

KEYWORDS: Artificial Intelligence; Regulation; Machine Learning; Clinical Trials; Clinical Research

SUMMARY: 1. Introduction – 2. The current regulatory landscape for conducting clinical trials in the EU – 2.1. The application of artificial intelligence to clinical research: stakeholder expectations – 2.2. The Artificial Intelligence Act: regulatory expectations – 3. The co-existence of the Clinical Trials Regulation (CTR) and the Artificial Intelligence Act (AIA) – 4. Conclusions.

1. Introduction

The application of emerging technologies, especially artificial intelligence (AI), to healthcare delivery and clinical research has the potential to enhance the capabilities of healthcare systems to offer high quality, evidence-based, data-driven, personalized medical solutions in a wide range of clinical fields including imaging, cardiology, psychiatry, oncology, intensive care, and

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neurology.[1] AI is also rapidly branching out into other clinical fields such as reproductive medicine,[2, 3] where patients can be offered personalized medical solutions together with personalized care, ensuring that innovative treatments take into consideration patients' personal perspectives and values to support informed decisions.[4] In such cases, AI can help in the process of informed decision-making by providing evidence-based data tailored to personal circumstances. Such patient assistance tools enabled by AI-powered devices can help in supporting and protecting fundamental human rights by enhancing the medical decision-making experience for patients. In particular, they can help patients and their care-givers by providing them with information relevant for their clinical cases and by enhancing their autonomous choices based on an understanding of the clinical context and treatment choices available to them. Healthcare professionals and clinical researchers also have many opportunities to benefit from AI input into their everyday practice. Clinicians can be supported by AI-powered tools in diagnostics, treatment, and treatment outcome modelling. Preliminary data shows that AI systems can read radiology images for breast cancer screening with more accuracy as compared to a single radiologist in a laboratory setting.[5] Moreover, public health has been benefiting from AI systems when predicting COVID-19 disease trends, infection rates, and infection peaks.[6] Clinical research is also benefiting from AI-powered tools in drug discovery by using AI for data processing, pattern identification, and conclusion modelling that would otherwise be time-consuming for human cognitive abilities to achieve.

Despite the increasing application of AI to clinical circumstances, there are no international laws in place that regulate such technologies. The Artificial Intelligence Act (AIA), proposed by the European Commission (EC) on 21 April 2021, is the first legislative proposal which offers a legal framework for AI use. This act was further specified by the Council of the European Union on 29 November 2021, which included clarifying the AIA's scope, the definitions of actors involved, prohibited AI practices, classification rules for high-risk AI systems, definitions of general-purpose AI systems not subject to AIA requirements, the delegation of legislative powers, and reporting.[7] This indicates the European Union's shift from a non-binding soft law approach to a legislative approach toward AI technologies. The AIA

[1] C. ZIPPEL, S. BOHNET-JOSCHKO, *Rise of Clinical Studies in the Field of Machine Learning: A Review of Data Registered in Clinicaltrials.Gov,* in *International Journal of Environmental Research and Public Health* 18,10,2021. https://doi.org/10.3390/ijerph18105072.

[2] N. ZANINOVIC, Z.ROSENWAKS, *Artificial Intelligence in Human in Vitro Fertilization and Embryology,* in *Fertility and Sterility* 114, 5, 2020, 914–20. https://doi.org/10.1016/j.fertnstert.2020.09.157.

[3] M. NASER, M. MN, L.H. SHEHATA, *Artificial Intelligence In Assisted Reproductive Technology Review* in *International Journals of Sciences and High Technologies* 25, 2, 2021, 507–11.

[4] J. JENKINS ET AL., *Empathetic Application of Machine Learning May Address Appropriate Utilization of ART,* in *Reproductive BioMedicine Online* 41, 4, 2020, 573–77. https://doi.org/10.1016/j.rbmo.2020.07.005.

[5] K. FREEMAN ET AL., *Use of Artificial Intelligence for Image Analysis in Breast Cancer Screening Programmes: Systematic Review of Test Accuracy*, in *The British Medical Journal* 374, n1872, 2021. http://dx.doi.org/10.1136/bmj.n1872.

[6] L. WANG ET AL., *Artificial Intelligence for COVID-19: A Systematic Review* in *Frontiers in Medicine* 8, September 2021, 1–15, https://doi.org/10.3389/fmed.2021.704256.

[7] COUNCIL OF THE EUROPEAN UNION, "Proposal for a Regulation of the European Parliament and of the Council Laying down Harmonised Rules on Artificial Intelligence (Artificial Intelligence Act) and Amending Certain Union Legislative Acts - Presidency Compromise Text," *Interinstitutional File: 2021/0106(COD)* 14278/21 (2021), https://data.consilium.europa.eu/doc/document/ST-14278-2021-INIT/en/pdf (last visisted 24/03/2022).

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is expected to be a horizontal EU legislative instrument applicable to all AI systems available in the EU market. The proposal of the AIA suggests that the rules for AI available in the European Union (EU) market should be "human-centric, so that people can trust that technology is used in a way that is safe and compliant with the law, including respect to fundamental human rights".[8] This approach will help to ensure that all AI technologies aimed at EU users are developed and maintained in line with the European values and principles laid out in the EU Charter of Fundamental Rights.[9] The AIA proposal appears to be focused on protecting the already-existing fundamental rights of EU citizens embedded in other legislative documents, with enhanced attention on the safety of AI products through a risk-based approach. At the moment, the AIA is undergoing a two-year consultation process. There will also be a two-year transition period after the AIA comes into force.

Subsequently, the EU approach to AI regulation focuses on the excellence and safety of AI products while ensuring public trust in AI technologies by: encouraging research and development activities and safeguarding fundamental human rights; ensuring legal certainty for developers; facilitating investment and innovation; and preventing market fragmentation.[10] Such an approach is likely to support the establishment of a reflective equilibrium when balancing various stakeholder interests around the development, marketing, maintenance, and usage of AI systems. Under the current blanket term of an "AI system" used in the initial and updated AIA proposal, the techniques and approaches used to define an AI system entail a wide range of software-based technologies such as "machine learning", "logic and knowledge-based systems" and "statistical approaches, Bayesian estimation, search and optimisation methods"[11] which will certainly be applicable across multiple AI applications to healthcare practices and clinical research.

Therefore, this article will focus on the AIA proposal and its potential to support and nourish the protection of fundamental human rights, as well as the use of patient-centric technology in clinical research. The authors will compare the general principles laid out in the AIA and in the "Clinical Trial Regulation (EU No. 536/2014) on clinical trials on medicinal products for human use" (CTR) in order to evaluate what the proposed AI regulation will bring to multiple stakeholders – including sponsors, investigators, patients and society at large – in the clinical research field. This will be achieved by showing where these two regulatory documents support each other, where they drift apart, and whether there are gaps or dissonance between the requirements for clinical research. The authors will employ the

[8] European Commission, Artificial Intelligence Act, Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL LAYING DOWN HARMONISED RULES ON ARTIFICIAL INTELLIGENCE (ARTIFICIAL INTELLIGENCE ACT) AND AMENDING CERTAIN UNION LEGISLATIVE ACTS § (2021), https://op.europa.eu/en/publication-detail/-/publication/e0649735-a372-11eb-9585-01aa75ed71a1/language-en/format-PDF/source-205836026. (last visited 29/08/2021).

[9] Charter of Fundamental Rights of the European Union, *Official Journal of the European Union* 326, no. 26.10.2012 (2012): 391–407, http://data.europa.eu/eli/treaty/char_2012/oj. (last visited 24/03/2022).

[10] European Parliamentary Research Service, Initial Appraisal of a European Commission Impact Assessment: Artificial Intelligence Act, vol. July, 2021. https://www.europarl.europa.eu/RegData/etudes/BRIE/2021/694212/EPRS_BRI(2021)694212_EN.pdf. (last visited 29/08/2021).

[11] Council of the European Union, *Proposal for a Regulation of the European Parliament and of the Council Laying down Harmonised Rules on Artificial Intelligence (Artificial Intelligence Act) and Amending Certain Union Legislative Acts - Presidency Compromise Text.*

following research methods to evaluate potential future legislation affecting the crossover of AI and clinical research: 1) document analysis, both of the proposed AIA and of the already-adopted CTR that has been in effect since 31 January 2022; 2) comparative research of the above mentioned legislative documents, investigating the core principles and main aims laid out in them; 3) deductive and inductive reasoning, to evaluate and generalise the future impact of the proposed AI regulation on the clinical research landscape in the EU.

The main areas of the application of AI to clinical research were identified using both scientific literature and that of the clinical research industry. As such, the following groups of AI use were established: basic administrative and operational support; study design; investigator site identification; patient recruitment; early-stage disease studies; clinical monitoring; pharmacovigilance; *in silico* modelling; decentralised/remote clinical trials; and enhanced patient diversity, inclusion, and representation in clinical trials. Table 1 provides a description of the above-listed activities, specifying what they entail when conducting clinical research. Each AI application group is preliminary evaluated for its risk level as follows, as per the AIA: unacceptable risk; high risk; and low or minimal risk. The core guiding principles found in the AIA and the CTR that govern the above AI groups are also listed in Table 1.

2. The current regulatory landscape for conducting clinical trials in the EU

At the time of writing this article, there were 386 583 research studies taking place in 219 countries listed in the US National Library of Medicine Clinical Trials Registry.[12] The EU Clinical Trials Register displayed 40 324 clinical trials taking place in the EU member states and in the European Economic Area (EEA).[13] In the EEA, approximately 4 000 clinical trials are authorized every year, with each trial taking place in an average of two Member States, and with 61% of clinical trials sponsored by the pharmaceutical industry and 39% by non-commercial sponsors.[14]

Clinical trials take many years to complete, which, in a commercial setting, usually means collecting enough data to be able to demonstrate the safety, efficacy, and effectiveness of a new medicinal product, procedure, intervention, or medical device in order to apply for marketing authorization rights in a desired jurisdiction. In addition to scientific hurdles, operational and administrative processes can significantly affect the time it takes to complete a clinical trial. Therefore, the regulatory landscape is very important when selecting countries for conducting global, multi-centre clinical trials. The EU has a large population of potential clinical trial participants and well-established public healthcare sectors, which are attractive to commercial clinical trial sponsors. Nevertheless, the recent regulatory landscape, as directed by Clinical Trials Directive 2001/20/EC,[15] has become difficult to navigate because of the different requirements in each Member State. This has made obtaining regulatory and ethics approvals to conduct clinical trials in the EU time-consuming and costly due to each Member State

[12] US National Library of Medicine, *Clinical Trials Registry*, https://clinicaltrials.gov (last visited 29/08/2021).

[13] European Medicines Agency, *EU Clinical Trials Register*, https://www.clinicaltrialsregister.eu/ctr-search/search. (last visited 29/08/2021).

[14] European Medicines Agency, *Clinical Trials in Human Medicines*, 2021, https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials-human-medicines.

[15] European Commission, "Clinical Trials - Directive 2001/20/EC" (2001), https://ec.europa.eu/health/human-use/clinical-trials/directive_en. (last visited 29/08/2021).

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having their own processes and requirements for conducting clinical trials, and then making approval decisions in isolation from each other.[16] While Clinical Trials Directive 2001/20/EC presented some key improvements in patient safety, ethical soundness, and data reliability, it quickly became one of the most-criticised legislative documents. These critiques came from multiple stakeholders, including patients, industry, and academic researchers. The EU Monitor reports that following the implementation of Clinical Trials Directive 2001/20/EC the administrative costs for non-commercial clinical trial sponsors increased by 98%, industry sponsors faced an 800% increase in insurance fees, and the average delay for launching a clinical trial increased by 90% (or 152 days). Subsequently, the number of applications to conduct clinical trials in the EU decreased by 25% between 2007 and 2011.[17]

The above concerns led to the creation of the Clinical Trial Regulation (EU No. 536/2014), which was adopted by the European Commission on 16 April 2014 and was set to replace the still-applicable Clinical Trials Directive 2001/20/EC (until the end of transition period for CTR scheduled 31 January 2023), with the ambition of streamlining the clinical trials approval process. Its application, however, was significantly delayed while the functionality of the EU-wide Clinical Trials Information System (CTIS) was established, tested, audited, and released.[18] Problems were identified even before the adoption of Regulation EU No. 536/2014, citing the complexity of EU jurisdiction in relation to national jurisdictions and the challenges of cultural aspects shaping national clinical trial landscapes.[19] As predicted, the Clinical Trial Regulation (EU No. 536/2014) only came into effect on 31 January 2022 – almost ten years after its adoption. Nevertheless, it is likely to be faced with new problems arising from the use of new technological developments in clinical research.

The core focus of the Clinical Trial Regulation (EU No. 536/2014) is on administrative aspects surrounding the clinical trials approval system in the EU while ensuring the safety, dignity, and wellbeing of clinical research participants and the reliability and robustness of collected data. The proposed AIA has the potential to support this by laying out the regulatory framework for how technology can be used to support administrative processes.

Both the Clinical Trial Regulation (EU No. 536/2014) and the Artificial Intelligence Act, which is likely to be adopted as a Regulation, are of note here. The latter will have to work in concert with the General Data Protection Regulation (EU 2016/679) (GDPR), which was adopted on 14 April 2016 and came into effect on 25 May 2018. The GDPR (EU 2016/679) was not designed specifically for clinical trials, but its requirements govern clinical research activities in all Member States and set out the legally binding obligations of clinical trial sponsors and contract research organizations (CROs) who process the personal data of clinical trial participants who reside in the EU. The GDPR (EU 2016/679) has been seen as

[16] EU MONITOR, *Explanatory Memorandum to COM(2012)369 - Clinical Trials on Medicinal Products for Human Use,* 2012, https://www.eumonitor.eu/9353000/1/j4nvhdfdk3hydzq_j9vvik7m1c3gyxp/vj19rqf41bwf. (last visited 29/08/2021).

[17] EU MONITOR, *Explanatory Memorandum to COM(2012)369 - Clinical Trials on Medicinal Products for Human Use,* 2012.

[18] EUROPEAN MEDICINES AGENCY, *Clinical Trials in Human Medicines.*

[19] S. ATZOR, S. GOKHALE, M. DOHERTY, *Will the EU Clinical Trials Regulation Support the Innovative Industry in Bringing New Medicines Faster to Patients?,* in *Pharmaceutical Medicine* 27, 2, 2013, 75–82. https://doi.org/10.1007/s40290-013-0012-8.

a trailblazer for regulating AI applications in the clinical field,[20] but also suggests that the specificities of the rights of minors are taken into account as well as the complexity created by the participation of pregnant women in clinical trials, especially if they are minors.[21] It can be considered that the GDPR has imposed very important rights-based regulations that have been adopted by leading technology companies worldwide by making data protection a market label and the centre of their businesses.

It is essential to note that the GDPR is one of the core legislative documents influencing the governance of technology use and the conduct of clinical research in the EU. Therefore, the protection of human rights is ensured organically across EU legislation in line with the fundamental rights protected by the EU Charter of Fundamental Rights. The protection of the fundamental rights is not only relevant in regards to privacy and personal data protection. It is also essential when classifying AI systems as high-risk, because these rights include: the right to human dignity; respect for private and family life; the protection of personal data; consumer protection; the rights of persons with disabilities; the right to health and safe medical interventions.[22] Multiple harms can occur when privacy and data protection requirements are violated, especially when sensitive health data is fed into technological applications. There are many examples where technological applications fail to protect user privacy and adhere to data protection requirements – such as the Grindr dating app sharing information about their users' HIV status, or the Royal Free Hospital in the UK transferring hospital records to Google DeepMind without informing patients. Even well-intentioned technological interventions can have negative consequences on the data of subjects, such as applications tracking and escalating users' suicidal thoughts based on social media posts, or pharmacy users being targeted by marketing companies.[23]

2.1. The application of artificial intelligence to clinical research: stakeholder expectations

The key difficulties in setting up a clinical trial are: finding and contracting investigator sites with access to the patient population that meets the study protocol's inclusion criteria; and having enough patients enrolled within the desired timeline. Delays in patient recruitment timelines result in clinical trial cost increases, and sometimes lead to early trial termination due to low patient enrolment.[24] Therefore, continuous attempts have been made to optimise clinical trial design, analyse data,[25] and enhance patient recruitment through digital advertising outlets that can yield good results for the direct-to-

[20] M. Bourassa Forcier et al., *Integrating Artificial Intelligence into Health Care through Data Access: Can the GDPR Act as a Beacon for Policymakers?,* in *Journal of Law and the Biosciences* 6, 1, 2019, 317–35. https://doi.org/10.1093/jlb/lsz013.

[21] H. W. Dalrymple, *The General Data Protection Regulation, the Clinical Trial Regulation and Some Complex Interplay in Paediatric Clinical Trials,* in *European Journal of Pediatrics* 180, 5, 2021, 1371–79. https://doi.org/10.1007/s00431-021-03933-3.

[22] Council of the European Union; Charter of Fundamental Rights of the European Union.

[23] MedConfidential, *Major health data breaches and scandals*, accessed March 24, 2022, https://medconfidential.org/for-patients/major-health-data-breaches-and-scandals/. (last visited 24/03/2022)

[24] O. Johnson, *An Evidence-Based Approach to Conducting Clinical Trial Feasibility Assessments,* in *Clinical Investigation* 5, 5, 2015, 491–99. https://doi.org/10.4155/cli.14.139.

[25] D. Kelly, A. Spreafico, L. L. Siu, *Increasing Operational and Scientific Efficiency, in Clinical Trials* in *British Journal of Cancer* 123, 8, 2020, 1207–8. https://doi.org/10.1038/s41416-020-0990-8; M. Liu et al., *Innovative Trial Designs and Analyses for Vaccine Clinical Development,* in *Contemporary Clinical Trials* 100, January 2021, 106225. https://doi.org/10.1016/j.cct.2020.106225.

patient advertising of clinical trials depending on the indication and regulatory landscape.[26] It is expected that AI will help to decentralise clinical trials, bringing them to patients who would otherwise not have access to clinical research centres. Nevertheless, there must be agreement regarding the protection of fundamental rights between patients, investigator sites, and sponsors, with scientific and financial incentives provided for local and regional investigator sites to carry out high-quality research. Laboratory examinations should be formally certified so that the same methodologies and units are used and data are easily interoperable, easily accessed, or sent to the main research centre. Imaging modalities may also be decentralised, provided a standardised protocol is used for image acquisition and all exams are digitised, stored securely, anonymised, and easily accessed by the main research centre. Only essential study procedures, such as biomarker assessments or tumour biopsies, should be validated centrally for good scientific reasons. Additionally, in many countries and hospitals the delivery of cancer medication to a patient´s home has been expanded to more patients, clinical conditions, and treatments as a response to the ongoing COVID-19 pandemic. While not yet generalized in clinical trials, this could be considered in the future for some oral treatments after setting up protocols for drug delivery, accountability, and compliance monitoring.

Taking into account recent developments, AI could significantly help to reshape the clinical trial design process and enhance patient selection for participation in clinical trials by quickly analysing large patient databases, identifying ideal patients that meet all trial inclusion criteria[27]. Nevertheless, AI errors in clinical trial participants selection can lead to some potential health problems and subsequently compromise their right to health, including physical and mental wellbeing. Moreover, AI use can enable streamlining the operational processes of clinical trial management from the clinical research industry's perspective.[28] AI is also expected to make data collection more efficient, ensure data quality, support faster medical treatments, and hasten the development of medical devices by making the clinical research process more efficient, informative, and patient-centric.[29] AI has the potential for more accurate disease detection and can not only improve early diagnosis but can also help to avoid overdiagnosis, which can be just as dangerous to the patient as the disease itself.[30]

Moreover, AI and related technologies are not only used to support clinical trial design, data processing, and operations management; AI interventions are also being tested as part of medical interventions. Such clinical trials are run to identify the safest and most effective AI applications to healthcare by testing their safety, efficacy, and patient outcomes compared to the existing standards

[26] M. BRØGGER-MIKKELSEN ET AL., *Online Patient Recruitment in Clinical Trials: Systematic Review and Meta-Analysis* in *Journal of Medical Internet Research* 22, 11, 2020, e22179. https://doi.org/10.2196/22179.

[27] S. HARRER ET AL., *Artificial Intelligence for Clinical Trial Design,* in *Trends in Pharmacological Sciences* 40, 8 2019, 577–91. https://doi.org/10.1016/j.tips.2019.05.005.

[28] L. GLASS, G. SHORTER, R. PATIL, *AI in Clinical Development*, 2019. https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/ai-in-clinical-development.pdf. (last visited 29/08/2021).

[29] M. F. DOCKENDORF ET AL., *Digitally Enabled, Patient-Centric Clinical Trials: Shifting the Drug Development Paradigm,* in *Clinical and Translational Science* 14, 2, 2021, 445–59. https://doi.org/10.1111/cts.12910.

[30] G. FERRETTI, A. LINKEVICIUTE, G. BONIOLO, *Comprehending and Communicating Statistics in Breast Cancer Screening. Ethical Implications and Potential Solutions*, in *Prediction and Prognosis: Future Knowledge in Medicine* (European Association for Predictive, Preventive and Personalized Medicine), 2017, 30–41.

of care interventions. At this time, research and evidence as to whether AI interventions do improve patient outcomes and are cost-effective remain in their early stages.[31]

AI applications have great potential in streamlining data processing and operational aspects of healthcare delivery and clinical research at a low or minimal risk, as per the AIA's proposed classification of risk levels. As a result, the pharmaceutical, biotechnology, and contract research industries are working to incorporate new technologies in their workstreams to optimize clinical trial management processes by reducing the time and cost required to create, test, and bring new pharmaceutical products to the market. At this time, AI can offer the most benefit in enhancing the operational aspects of clinical trial design, investigator site identification, patient recruitment, pharmacovigilance data processing, clinical monitoring, and patient care.[32] Nevertheless, the continuously increasing number of applications of automated decision-making in medicine call for regulatory guidance at the national and international levels, and regulatory proposals are watched closely by multiple stakeholders. Some professional guidelines for reporting clinical trial results involving AI have already been published.[33] The SPIRIT-AI and CONSORT-AI guidelines stress the need for data robustness and clear indications as to whether AI is being tested in an ideal environment or in real-word conditions in order to differentiate between those AI interventions which work in ideal conditions and those that can reliably be transferred to a real-word setting. Nevertheless, AI also offers an opportunity to make clinical trials cheaper, faster, safer, and easier to scale by allowing an *in silico* modelling environment, which could potentially replace the need for placebo groups in clinical trials.[34]

2.2. The Artificial Intelligence Act: regulatory expectations

It is expected that AI technologies will be able to support the decentralisation of clinical trials, which has been accelerated by the COVID-19 pandemic. The guidance of the European Medicines Agency (EMA) for clinical trials during the COVID-19 pandemic accepts that laboratory exams, imaging, or other diagnostic tests can be performed locally, outside the research centre,[35] which reduces the time and cost of otherwise resource-intensive procedures. There are good reasons to keep this practice beyond the pandemic, including the lack of evidence supporting the superiority of central testing over local, at least for routine procedures. Many diagnostic exams can be performed under the same conditions in different institutions, with proper certifications, without undermining the quality of data. This patient-

[31] H. IBRAHIM ET AL., *Reporting Guidelines for Clinical Trials of Artificial Intelligence Interventions: The SPIRIT-AI and CONSORT-AI Guidelines*, in *Trials* 22, 1, 2021, 1–5. https://doi.org/10.1186/s13063-020-04951-6.

[32] L. GLASS, G. SHORTER, R. PATIL, *AI in Clinical Development*.

[33] IBRAHIM ET AL., *Reporting Guidelines for Clinical Trials of Artificial Intelligence Interventions: The SPIRIT-AI and CONSORT-AI Guidelines.*

[34] F. PAPPALARDO ET AL., *In Silico Clinical Trials: Concepts and Early Adoptions*, in *Briefings in Bioinformatics* 20, 5, 2019, 1699–1708. https://doi.org/10.1093/bib/bby043; A. BADANO, *In Silico Imaging Clinical Trials: Cheaper, Faster, Better, Safer, and More Scalable*, in *Trials* 22, 1, 2021, 1–7. https://doi.org/10.1186/s13063-020-05002-w.

[35] EUROPEAN MEDICINES AGENCY, GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC, Human regulatory, 2021, https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice#guidance-on-clinical-trial-management-during-the-covid-19-pandemic-section. (last visited 29/08/2021).

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friendly policy may reduce disparities in access to clinical trials for patients living in remote areas without immediate access to major research hospitals.

The potential impact of the AIA on the applications of AI to clinical research in the EU can be evaluated by looking at what types of clinical research activities are already, or have the potential to be, supported by AI technologies. Moreover, the regulatory impact will become clearer when actual applications of AI to clinical research are reviewed by national regulatory authorities and ethics committees. Nevertheless, some promising applications of AI to clinical research have low or minimal risk – such as basic administrative and operational support, study design, investigator site identification, early-stage disease studies, and enhanced patient diversity, inclusion, and representation in clinical trials – and will likely not require any prior approval to be used in clinical trials. This space is closely monitored by trial sponsors, clinical trial management organisations, technology companies developing and selling specific services, regulatory authorities, private and academic investigator sites, and patient organisations. Approvals for the above applications might not be required because AI technologies may be used for faster data processing, quick pattern and correlation identification, and administrative process optimisation. This is in line with the updated version of the AIA, which suggests that: "AI systems that are able to perform generally applicable functions such as image/speech recognition, audio/video generation, pattern detection, question answering, translation etc. – should not be considered as having an intended purpose […]. Therefore, the placing on the market, putting into service or use of a general-purpose AI system, irrespective of whether it is licensed as open-source software or otherwise, should not, as such, trigger any of the requirements or obligations of this Regulation".[36]

Moreover, a rather fluid definition of "artificial intelligence system (AI system)" in the AIA can serve as a double-edged sword. On one hand, a broad definition of AI can encompass multiple applications of AI that the everchanging market will raise in the future, and offer regulation to protect fundamental rights. On the other hand, this can result in further disagreements and hold back innovation by creating uncertainty among developers and users due to a broad definition of an AI system, which was initially described as a "software that is developed with one or more of the techniques and approaches listed in the Annex I and can, for a given set of human-defined objectives, generate outputs such as content, predictions, recommendations, or decisions influencing the environments they interact with" [37] but later specified as a system that "receives machine and/or human-based data and inputs, infers how to achieve a given set of human-defined objectives using learning, reasoning or modelling implemented with the techniques and approaches listed in Annex I, and generates outputs in the form of content (generative AI systems), predictions, recommendations or decisions, which influence the environments it interacts with".[38]

Under the current definition of an AI system, it is possible that even methods and systems currently in everyday use might fall under the AIA regulation in the future. Hence, the specification and addition of general-purpose AI use to the AIA text appears to make attempts to address such problems. AI techniques and approaches referred to in the above definition include machine learning approaches using a wide variety of methods such as deep learning, logic-based and knowledge-based approaches,

[36] Council of the European Union.
[37] European Commission, *Artificial Intelligence Act*.
[38] Council of the European Union.

statistical approaches, Bayesian estimation, and search and optimisation methods. This definition covers many tools already in use for clinical research management and data processing. For example, most clinical research centres have patient databases which can range from paper records to easily searchable electronic records with multiple search options. Such a simple tool has the potential to be considered an AI system and, depending on how the search function is programmed, could easily shift back and forth between the categories of low or minimal risk to high risk. Thus, classifying such uses of AI as general use could offer a solution. The overregulation of AI use would be an undesired and unintended consequence of AIA because it would complicate already-functioning systems with additional regulatory requirements.

The application of AI to clinical monitoring, pharmacovigilance, *in silico* modelling, and decentralised/remote clinical trials management has the potential to fall into the high-risk group depending on the extent to which AI technologies are chosen for use. All four areas require attention to the health and safety of clinical research participants, which AI can help to ensure by simplifying the administration and data analysis tasks. However, it can also endanger the safety of research participants and breach their fundamental rights if some safety decisions are delegated to AI systems without sufficient human oversight. The current AIA proposal is relatively obscure as far as the applications of AI to clinical research are concerned. Due to the very broad definition of an AI system, it will likely be very difficult to determine from the start of the development process of such an AI system when it is going to cross the boundary of high-risk, and when it might become an unacceptable risk. Nevertheless, such quandaries can likely be addressed by combining risk-based and rights-based approaches to the application of AIA in practice.

Furthermore, patient recruitment to clinical trials is also likely to benefit from AI technology. Hence, AI support for patient recruitment can cover all risk categories based on how AI technologies are applied, where they are used, and what is considered AI in general. There are multiple areas where the risk will be low or minimal, but the boundaries can be crossed easily where AI is used for targeted advertising based on social characteristics. For example, using AI to predict if clinical research participants will be compliant with study procedures based on their social behaviour or personality characteristics might linger between unacceptable and high risk. Restrictions on examples of the latter, such as social scoring, were limited to public authorities in the original AIA proposal, but have been updated in a subsequent version to include AI systems employed by private actors.[39] How the above requirement will be implemented in practice remains to be seen. Table 1 summarises the main areas of the application of AI to clinical research, core guiding principles in AIA and CTR, and the rights which might be affected by applying AI in these areas. As discussed above, the risk levels were assigned to each application area based on what each AI application is expected to deliver. For example, areas where AI is used for administrative data processing in order to make the overall processes faster were allocated to the low or minimal risk category, while clinical data processing with the intention of streamlining clinical decisions, risk, and patient safety management were put into the potentially high-risk category.

Table 1. The application of AI to clinical research: risk levels and core guiding principles in the Artificial Intelligence Act and the Clinical Trial Regulation.

[39] COUNCIL OF THE EUROPEAN UNION.

Area of AI application to clinical research	Types of activities covered by this AI application	Risk level as per the Artificial Intelligence Act	Core guiding principles in the Artificial Intelligence Act	Core guiding principles in the Clinical Trial Regulation (EU No. 536/2014)	Rights affected by applying AI in this area
Basic administrative and operational support	Administrative data processing	Low or minimal risk	Accuracy, reliability, robustness, cybersecurity, transparency, accountability, democratic processes	Protection of rights	Protection of personal data, consumer protection
Study design	Scientific data processing, identifying patterns, making suggestions for the optimal study design	Low or minimal risk	Accuracy, reliability, interpretability, robustness, accountability, cybersecurity, transparency, freedom, representativeness, safety	Data reliability and robustness	Protection of personal data, rights of persons with disabilities, right to health and safe medical interventions
Investigator site identification	Administrative data processing, making suggestions for most suitable institutions	Low or minimal risk	Accuracy, reliability, robustness, cybersecurity, transparency, equality, justice, freedom, security, democratic processes, representativeness	Protection of rights	Protection of personal data, consumer protection
Patient recruitment	Personal and clinical data processing, targeted advertising, making predictions for which patients will be suitable and reliable clinical research participants	(Potentially) high risk with some unacceptable aspects	Accuracy, reliability, interpretability, robustness, accountability, cybersecurity, transparency, dignity, non-discrimination, equality, justice, freedom, security, democratic processes, representativeness, safety, fundamental rights	Protection of rights, safety, dignity and well-being	Right to human dignity, respect for private and family life, protection of personal data, consumer protection, rights of persons with disabilities, right to health and safe medical interventions
Early-stage disease studies	Personal data processing, making predictions for which patients might have early-stage diseases	Low or minimal risk	Accuracy, reliability, interpretability, robustness, accountability, cybersecurity, transparency, democratic processes,	Protection of rights, safety, dignity and well-being	Protection of personal data, rights of persons with disabilities, right to health and safe medical interventions

	which cannot be detected by human doctors		representative-ness, safety		
Clinical monitor-ing	Administra-tive, personal, and clinical data pro-cessing, risk prediction, automated risk manage-ment	(Potentially) high risk	Accuracy, reliabil-ity, interpretabil-ity, robustness, accountability, cy-bersecurity, trans-parency, equality, justice, freedom, security, environ-mental sustaina-bility, safety	Protection of rights, safety, dig-nity and well-be-ing; Data reliability and robustness	Right to human dignity, protection of personal data, right to health and safe medical inter-ventions
Pharmacovigi-lance	Administra-tive, personal, and clinical data pro-cessing, risk prediction, automated risk manage-ment	(Potentially) high risk	Accuracy, reliabil-ity, interpretabil-ity, robustness, accountability, cy-bersecurity, trans-parency, demo-cratic processes, safety	Protection of rights, safety, dig-nity and well-be-ing; Data reliability and robustness	Right to human dignity, right to health and safe medical interven-tions
in silico model-ling	Clinical data processing, building dis-ease models which could replace the need for the placebo arm	(Potentially) high risk	Accuracy, reliabil-ity, interpretabil-ity, robustness, accountability, cy-bersecurity, trans-parency, demo-cratic processes, environmental sustainability, rep-resentativeness, safety	Protection of rights, safety, dig-nity and well-be-ing; Data reliability and robustness	Protection of per-sonal data, con-sumer protection, workers' rights, rights of persons with disabilities, right to health and safe medical inter-ventions
Decentral-ised/remote clinical trials	Administra-tive, personal, and clinical data pro-cessing, risk prediction and management	(Potentially) high risk	Accuracy, reliabil-ity, interpretabil-ity, robustness, accountability, cy-bersecurity, trans-parency, equality, justice, demo-cratic processes, environmental sustainability, safety, fundamen-tal rights	Protection of rights, safety, dig-nity and well-be-ing; Data reliability and robustness	Right to human dignity, protection of personal data, consumer protec-tion, workers' rights, rights of persons with disa-bilities, right to health and safe medical interven-tions
Enhanced pa-tient diversity, inclusion, and	Personal and clinical data processing,	Low or minimal risk	Accuracy, reliabil-ity, interpretabil-ity, robustness, accountability,	Protection of rights, safety, dig-nity and well-be-ing	Respect for pri-vate and family life, protection of personal data,

representation in clinical trials	targeted advertising		cybersecurity, transparency, dignity, non-discrimination, equality, justice, democratic processes, freedom, security, representativeness, safety, fundamental rights		consumer protection, rights of persons with disabilities, right to health and safe medical interventions

3. The co-existence of the Clinical Trials Regulation (CTR) and the Artificial Intelligence Act (AIA)

The goal of Clinical Trials Regulation (EU) No. 536/2014 is to create an environment that is favourable to conducting clinical trials, with the highest standards of safety for clinical research participants and increased transparency of trial information, emphasising that patients' rights and interests – such as the protection of privacy, the option to withdraw from clinical trials without obligation to justify such a decision, and the safety of experimental medicinal products – should always be prioritised. The CTR requires all information stored in a database to be publicly available, unless exempted in order to protect: personal data; commercially confidential information, in particular the marketing-authorisation status of the medicine; confidential communication between Member States in the preparation of their assessment; the supervision of clinical trials by Member States. Such goals align with all of the specific objectives outlined in the AIA impact assessment, which include: ensuring safety and adherence to current rules with respect to fundamental rights and EU values; providing legal certainty and facilitating investment; enhancing governance and enforcement of existing rules; and preventing market fragmentation by facilitating a single market for lawful, safe, and trustworthy AI applications. Despite aiming to be robust, the AIA offers a flexible legal framework, adopting a risk-based regulatory approach without unnecessary restrictions to trade, innovation, or investment. This is welcome news for researchers, clinical trial managers, and administrators because it will likely allow diverse applications of AI to many different clinical research areas with further compliance requirements being provided by industry standards or technical specification documents.

On the other hand, the rules laid out in the CTR are quickly becoming outdated in light of the perspective of currently available technology, or are likely to require clarification as to what they are going to permit and how. Especially in the rapidly-developing landscape of clinical trial decentralisation, questions remain regarding, for example, electronic informed consent for participation in clinical trial: will it still be the case that using a mobile application constitutes informed consent given in writing, or will the mobile application need to have audio and video enabled features? In addition, will graphic and/or video aides replace the time spent with the clinical trial clinicians reviewing the informed consent form and getting potential clinical trial participant's questions answered. While the AIA will likely prohibit targeting potential clinical research participants based on protected characteristics – although those characteristics might be desired in the research participant pool to ensure diversity of clinical trial participants and the representation of a real-world population – as required by CTR Article 5 (b) and (c),

some types of patient recruitment activities will likely fall within the low or minimal risk category, and will help to find qualified patients in a shorter timeframe. It is possible that a rights-based approach stemming from the GDPR will lend a hand in ensuring that the fundamental rights of clinical research participants are protected.

It is also likely that multiple AI applications that fall within the low or minimal risk category will support the implementation of the requirements laid out in the CTR by making its application across the EU feasible. Nevertheless, the CTR does not specifically address how new technological developments should be handled other than to state that those technological developments should be taken into consideration. Similarly, the AIA does not specifically lay out any rules for the application of AI to clinical trials. Therefore, it is only possible to compare the co-existence of these two documents though the lens of the general principles found in both of them. Both documents are expected to support each other horizontally, which appears possible due to the similarity of the general principles listed in each of them.

The AIA appears to endorse a values-based approach to the AI regulation, which stresses the importance of human dignity, equality, human rights, and the rule of law embedded in the EU Charter of Fundamental Rights. The CTR also stresses the importance of the rights, safety, dignity, and well-being of clinical research participants and the availability of reliable and robust clinical research data which echoes the privacy and data protection requirements laid out in the GDPR. Clinical researchers are already familiar with a similar set of values expressed through the principles of biomedical ethics, including: respect for personal autonomy, non-maleficence, beneficence, and justice.[40] While it remains to be seen how the AIA will function in practice, a flexible, risk-based approach to AI regulation will allow the rapid application of AI technologies across a wide spectrum of clinical research activities. Therefore, as much as AI has a potential to streamline some clinical research processes, it potentially will pose some challenges because its risk level can depend on how and with what purpose AI tools are used.

Despite the overlapping principles which correspond seamlessly to fundamental EU values, some concerns remain, especially in relation to the definition of what will be considered an AI system to which the rules laid out in the AIA will apply. However, it appears that efforts are being made to clarify the definition of an AI system to limit the broad application of AIA by allowing general-use AI systems to function without the obligations laid out in the AIA. A broad definition of an AI system has the potential to engulf many aspects of everyday data processing under the AIA requirements, which could compromise the aim of the AIA to create a competitive market place, facilitate innovation and investment, and ensure legal certainty. Were the definition of an AI system to remain as broad as it is in the initial proposal, it is possible that additional compliance costs and administrative burdens would make the EU less attractive to investors and businesses alike, not only stagnating innovation and the development of AI tools but also making it more difficult to stay compliant when using existing tools which ease the burden of administrative and data processing tasks in clinical research.

[40] T. L. BEAUCHAMP, J. F. CHILDRESS, *Principles of Biomedical Ethics*, 8th edition New York, 2019.

While patient safety, health, and privacy are key aspects to be protected by regulators, some authors suggest that there should be a careful balance between the latter and progress in innovation.[41,42] The AIA demonstrates an intent to support technological innovation by balancing the protection of fundamental rights and supporting the creation of a competitive single market for AI products, and the CTR is aimed at easing the administrative burden when submitting regulatory applications for clinical trial approvals.

After this initial evaluation, the AIA and the CTR do appear to support each other and do not display obvious gaps or dissonance in what they require from clinical research stakeholders. However, problematic aspects of implementing the requirements of both documents will likely become more apparent once they both fully come into effect. The most significant pitfall appears to be lurking in the definition of AI systems as currently worded in the AIA, which could compromise the intention to have a flexible, risk-based regulatory framework for lawful, safe, and trustworthy AI applications. Nevertheless, this definition could also act a safeguard for protecting fundamental rights across a wide range of future developments.

In addition, it remains to be seen how well it is possible to balance economic interests driven by innovation and the need to remain competitive on a global scale against patient and public trust in AI technologies. Would patients agree to take part in clinical trials where AI plays a role beyond administrative efficiency and data processing? Will there be enough qualified patients agreeing to take part in clinical trials to adequately test AI interventions? Such research is still in its infancy, but most recent scholarly contributions suggest that patients should have the right to reject diagnostic decisions made by AI and seek a second opinion from a human doctor.[43] The latter would be in line with their fundamental rights, as outlined in the EU Charter of Fundamental Rights.

4. Conclusions

Harmonized regulation on the use of AI in clinical research is eagerly awaited by all stakeholders because it will help to ensure that AI technologies are safe and trustworthy, support innovation and investment in the EU market, and provide some legal certainty for businesses working to make clinical trials faster, cheaper, and more efficient. This, ultimately, will benefit both patients and the general public. This comparative analysis shows that the proposed Artificial Intelligence Act and the Clinical Trials Regulation are likely to work in concert and supplement each other in clinical research regulation in the EU, based on overlapping or corresponding principles referenced by each document. It is also likely that multiple AI applications falling within the category of low or minimal risk will support the implementation of requirements laid out in the Clinical Trials Regulation by making the application of AI feasible across the EU.

[41] I.G. COHEN ET AL., *The European Artificial Intelligence Strategy: Implications and Challenges for Digital Health*, in *The Lancet Digital Health* 2, 7, 2020, 376–79, https://doi.org/10.1016/S2589-7500(20)30112-6.

[42] G. MALIHA et al., *Artificial Intelligence and Liability in Medicine: Balancing Safety and Innovation*, in *The Milbank Quarterly* 99, 3, 2021, 629–47, https://doi.org/10.1111/1468-0009.12504.

[43] T. PLOUG, S. HOLM, *Right to Contest AI Diagnostics*, in *Artificial Intelligence in Medicine*, 2021, 1–12. https://doi.org/10.1007/978-3-030-58080-3_267-1.

The current Artificial Intelligence Act proposal is relatively obscure as far as the applications of AI to clinical research are concerned. Due to the relatively broad definition of an AI system, it will likely be very difficult to determine during the process of developing AI systems when they cross the boundaries of high-risk, and when they might bear an unacceptable risk. There are signs that this will be addressed in the forthcoming revisions of the AIA, which weather down the concern of this being a potential obstacle for meaningful implementation and the creation of a competitive marketplace for artificial intelligence products in the EU. Overlapping principles which correspond seamlessly to the fundamental EU values will help to ensure that fundamental rights are protected.

Furthermore, limitations related to the different health systems and cultural components of national jurisdictions in different EU counties will likely continue to be a hurdle for legal certainty where regulatory and ethics approvals for clinical trial conduct are concerned. This is because the Clinical Trials Regulation offers a unified system for processing clinical research approvals but does not impose that each Member State should take the same decision when reviewing national applications to conduct clinical research. Therefore, national differences will likely remain in regards to which clinical trials are issued approvals, and possibly even which AI systems are permitted due to the easy shift between risk levels outlined in the Artificial Intelligence Act that is currently possible. However, well-established GDPR practices cementing rights to privacy and personal data protection have the potential to support and enforce the seamless application of the requirements of both the CTR and the AIA.

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