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Artificial intelligence in clinical trials in the UK and EU

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This article explores how artificial intelligence has the potential to transform the clinical trial process in the UK and the EU. The article examines the legal and regulatory issues relating to the use of AI in clinical trials, as well as the attendant difficulties that can occur.

According to data from the European Federation of Pharmaceutical Industries and Associations, the average length of time to bring a drug to market is quoted as being 12 to 13 years from the first synthesis of the new active substance and, in 2014, cost an estimated EUR1.926 million (see EFPIA: The Pharmaceutical Industry in Figures 2023). That cost is significantly higher ten years later. In addition, only one or two of every 10,000 substances make it to market. Anything that streamlines this process, and increases the efficacy and speed in which drugs can be brought to patients, will be welcomed by industry and patients alike. Artificial intelligence (AI) may offer that hope.

We are at a stage of exploration about the use of AI, where companies want to use the new technology, and regulators are racing to develop a framework to offer both guidance to industry and enable them to assess the AI technology. In relation to clinical trials, there are many examples of uses of AI, many of which are supportive, or help to speed up the clinical trial or its recruitment. However, we are increasingly seeing uses where the AI has a role in the clinical decision-making.

Clinical trials are already associated with a detailed legal and regulatory framework, and the addition of AI only increases the complexity of ensuring compliance with the regulatory requirements, and raises a number of important ethical and regulatory concerns, such as:

- How the AI is regulated.
- The quality and reliability of the data generated.
- The protection of the safety, health and fundamental rights of clinical trial patients, including data privacy considerations.

There are also more fundamental concerns from the authorities about whether they can understand and rely on what the AI is doing. Similarly, a key obstacle to the introduction of AI in clinical trials is gaining users' trust given that the methods for generating and processing information and the function of the AI software is usually unknown to the healthcare professionals and patients.

There is currently limited specific legislation or guidance on the use of AI in clinical trials. Instead, AI is regulated under a range of other regimes, and the authorities are starting to publish specific guidance on AI. This guidance provides a framework for developers and an understanding of how the authorities are likely to view the use of AI in clinical trials and to assess the data as part of the authorisation process. However, we are still at the phase of most AI technologies having to navigate the regulatory framework afresh each time, and the authorities are developing the framework as they assess these products. It is hoped the guidance will become more concrete in time for many companies to include it in their development plans.

This article sets out some of the life sciences legal and regulatory parameters around the use of AI in clinical trials, and some of the difficulties. There are of course also ethical and technological issues with such technology, where guidelines and principles are fast developing, but those are outside the scope of this article.

The use of AI in clinical trials

Clinical trials are designed to generate often large quantities of data to assess the safety and efficacy of a new investigational medicinal product. Given the large amounts of data that must be generated and analysed, and the number of different parameters that may be relevant, large language models (LLMs) and machine learning are increasingly being used to streamline that process. There are already many examples where AI has been used in clinical trials. At present, these uses are

usually supportive to the clinical trial, or to help identify trends in data that is generated in the "usual" clinical manner.

For example, AI has been used to identify or optimise possible target molecules to take into clinical testing, as reported in the media earlier this year in relation to the identification of abaucin as a new antibiotic. Also earlier this year, a drug generated by AI from Insilico Medicine entered Phase II clinical trials. AI is also used to scan patient records and help to identify patients who may be eligible for a trial, such as Amgen's Analytical Trial Optimization Module AI platform, known as ATOMIC. See Insight: Big Pharma bets on AI to speed up clinical trials, reuters.com, 22 September 2023. This greatly increases the speed and accuracy of patient recruitment and thereby reduces costs and patient drop-out rates. AI is also being used to help analyse adverse event data and to identify potential safety signals in trials more quickly.

However, the potential of AI and LLMs to generate data, or to cut down the amount of clinical data required, means the uses of AI are increasing. Synthetic data and in silico clinical trials (virtual clinical trials using computer simulations) are already being used in clinical research, and companies are using synthetic control arms (an external control using existing patient data rather than data from patients involved in the trial) to speed up development time. These synthetic control arms are currently made up of real-world data from electronic health records or extrapolation of existing data, rather than fully AI-generated dataset. For example, a number of clinical trial companies offer "synthetic control arm" services, such as Altis Labs, where the dataset is made up of patients in their databases and the AI system chooses control patients that match the patients in the trial (see Altis Labs: Altis Labs Launches Digital Twins for Clinical Trials with Global Biopharmaceuticals & Leading Research Institutions (23 August 2023)). Similarly, there are companies that offer "digital twins" to generate predicted outcomes using AI for the patients that are already enrolled in the trial. The European Medicines Agency (EMA) has provided an opinion on the use of trial subjects' AI generated predicted outcomes as a placebo in clinical trials, such as UNLEARN's Prognostic Covariate Adjustment (see European Medicines Agency: Qualification opinion for Prognostic Covariate Adjustment (20 September 2022)).

The activities that the AI performs are expanding. Exscientia, an AI-led precision medical company, published its EXALT-1 clinical study in 2021, which was reportedly the first prospective interventional study whereby predictions made by an AI platform proposed the most effective therapy for late stage haematological cancer patients based on testing drug responses ex vivo in the patients' tissue samples (see Exscientia: Publication of EXALT-1 Trial in Cancer Discover Demonstrates First AI-Supported Functional Precision Medicine Platform to Improve Cancer Treatment Outcomes (11 October 2021)). This moves the AI from a tool to assist with speeding up clinical trials to a decision-making tool that determines treatment for patients. As expected, the regulatory regime and related compliance risks around such uses are significantly higher.

Legal and regulatory issues associated with the use of AI in clinical trials

The regulation of AI in clinical trials

The use of AI is permitted under EU and UK regulatory guidelines, although is not specifically addressed in the legislation or guidance on clinical trials. Instead, AI is regulated by a variety of existing legal and regulatory regimes that need to be applied to the new technology. Some of these are set out below. As these technologies continue to be used, it will become increasingly important for the authorities to establish international harmonisation of the principles to be followed, and to use a multidisciplinary approach to take into account the different factors applicable to AI.

Legal requirements for AI

The lack of a specific legal framework is likely to change in the future, as AI-specific legislation is being considered in the EU and the UK is developing regulatory guidelines.

In the EU, the European Commission published a proposal for an AI Act in April 2021, that sought to comprehensively regulate AI systems in the European Union (see European Commission: Proposal for a Regulation laying down harmonised rules on artificial intelligence (21 April 2021)). The proposed AI Act takes a risk-proportionate approach and categorises four levels of AI systems, ranging from "no or minimal risk", to "limited risk", "high risk", and finally, "unacceptable risk". Medical devices will be classed as "high risk", and would therefore be subject to a set of requirements proportionate to this risk before the products are placed on the market and throughout the product life cycle. For more details, see Regulation laying down harmonised rules on artificial intelligence (Artificial Intelligence Act): legislation tracker.

In December 2022, the Council of the European Union adopted its common position on the proposed AI Act

(see 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 (25 November 2022)), and in June 2023, the European Parliament agreed its own amendments to the proposal (see Legal update, Artificial Intelligence Regulation: European Parliament adopts negotiation mandate). The EU institutions have now entered a "trilogue" process to negotiate the text of the legislation, with the hope an agreement can be reached so it can be adopted at the end of this year. See Practice note, Legal aspects of artificial intelligence: AI regulation in the EU.

A recent draft of the proposed EU AI Act acknowledges the need for alignment of the AI Act and the rules on medical devices, and the need to avoid duplication between sectoral legislation and AI provisions. However, there is no exemption for medical devices or medical research. While there is an exemption under the proposal for "research, testing and development activities", this relates to research into the AI itself, and not the use of AI in any research setting. Therefore, as it currently stands, AI used within a clinical trial in the EU will need to comply with the proposed EU AI Act.

In contrast, the UK has, so far, taken a different approach that is intended to focus on promoting innovation and experimentation, whilst maintaining a light touch in terms of regulation. In July 2022, the UK government published a policy paper on regulating AI (see Legal update, Government policy paper and call for views on regulation of artificial intelligence). The government proposed to establish a pro-innovation framework of principles for regulating AI, while leaving regulatory authorities discretion over how the principles apply in their respective sectors, which in this case would be the Medicines and Healthcare products Regulatory Agency (MHRA) (see below for the MHRA position on AI). Annex A to the policy paper sets out principles that the regulatory authorities should take into account when developing such guidance, including:

- Safety, security and robustness.
- Appropriate transparency and explainability.
- Fairness.
- Accountability and governance.
- Contestability and redress.

The government intends the framework to be "proportionate, light-touch and forward-looking" to ensure that it can keep pace with developments in these technologies. The government's white paper on AI was published on 29 March 2023 and set out its proposals to regulate AI in a pro-innovation manner in line with the policy paper (see Practice note, Artificial Intelligence: UK regulatory developments and Legal update, Government publishes AI white paper: a pro-innovation approach to AI regulation). However, this approach has been criticised, with some stakeholders believing legislation should be introduced given the ever-pervasive uses of AI, and to keep in line with developments in the EU and initiatives in the US.

As yet, there are no legislative provisions on AI in either the EU or UK. While this gives some flexibility to companies who wish to use AI in clinical trials, it also leads to uncertainty, and ultimately to delays during the regulatory process unless the sponsor has compelling data on how the AI operates.

Classification of AI as medical device

As well as general legislation on AI, where the technology is used within healthcare and in clinical trials, developers also need to consider the rules on medical devices. AI will not be classed as a medical device in all cases, but often a CE marking or UK Conformity Assessment (UKCA) mark will provide some comfort to users that the technology meets certain standards. This standard is also often required to make use of some of the market access schemes that are available in various countries for digital technologies (pricing and reimbursement of digital technologies is outside the scope of this article).

Depending on its functionality, and its intended purpose, AI technologies may fall within the definition of medical device in the EU or the UK. For example, AI used for a medical purpose, such as diagnosis or prediction of a disease, would qualify as a medical device. To determine whether a medical purpose exists, the specific functions of the AI must be reviewed in the light of the definitions in:

- Regulation (EU) 2017/745 on medical devices (MDR).
- Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR).
- The European Medical Device Coordination Group guidance document on qualification and classification of software in the MDR and IVDR (MDCG guidance) (see Europa.EU: MDCG 2019-11 guidance on software qualification and classification).
- The UK Medical Devices Regulations 2002 (*SI 2002/618*) (MDR 2022). Although the EU MDR does not apply in Great Britain, it is applicable in Northern Ireland, and the previous EU Medical Device Directives (the Medical Devices Directive (*93/42/EEC*) (MDD), the Active Implantable Medical Devices Directive (*90/385/EEC*) (AIMDD) and the In Vitro Diagnostic Medical Devices Directive (*98/79/EC*) (IVDD)), on which the UK legislation is based, included

similar considerations in relation to the classification of software and AI as medical devices.

- The MHRA software flowchart guidance (see MHRA: Guidance: Medical device stand-alone software including apps (including IVDMDs)).

AI systems that analyse large amounts of data to develop knowledge about a disease or condition, but do not decide on treatment options for an individual patient, will not necessarily be considered as having a medical purpose, and therefore would not be deemed a medical device. In contrast, AI aimed at enhancing or improving clinical diagnosis or informing, or making, decisions on treatment is likely to be considered as having a medical purpose. Further, where the AI is part of the clinical decision-making, this is likely to lead to the AI falling within a higher classification of medical device, meaning more stringent regulatory requirements will apply. This assessment needs to be undertaken with a review of the functionality of the technology, the claims made about the technology as well as the output and how that output will be used and will determine the level of regulatory oversight that is required.

The regulatory framework for medical devices sets out requirements for the development, manufacture and commercialisation of the products. There is therefore a potential conflict with the proposed EU AI Act, which seeks to do the same for AI technologies. A number of industry groups have raised concerns about the potential for overlapping, and even conflicting, requirements that will need to be met and the difficulties this will place on innovation, but, as set out above, there is no exemption for AI medical devices.

A further point to consider is that where the AI is classified as a medical device, it will need to undergo clinical investigations or performance evaluation before obtaining a CE/UKCA mark to be placed on the market. Where the AI is used in a clinical trial, the clinical trial may need to be undertaken jointly with the clinical investigation for the AI. This is envisaged in the guidance, but in practice means two sets of applications must be made, and approved, and two sets of data generated for the final report. This is already a complicated process given the new rules in the EU on clinical trials and medical devices. Where there is an AI element as well, which is a relatively novel inclusion into the clinical investigation frameworks, sponsors will need to build in time to the trial set-up process to respond to questions from the authorities.

Guidance on the use of AI in clinical trials

There is limited regulatory guidance on the use of AI in clinical trials. Instead, the general rules apply, and it is for the sponsor of the trial to demonstrate to the authorities that the AI technology is robust, is compliant with Good Clinical Practice (GCP) and can be relied on. AI technology, and AI-generated data, will not remove the need for in-person clinical trials in the near future, but there is definitely scope for these technologies and synthetic data to complement clinical data and for the two to be used together. The key will be data integrity, which is important in all trials, and ensuring that the data generated about the investigational medicinal product is sufficiently robust to demonstrate that the product is safe and effective. This will include information on what data sets the AI is trained on and how the AI processes and uses such data. In the last couple of years, GCP inspections conducted by the MHRA and the EU member states' authorities have increasingly focused on the validation and qualification of software used in clinical trials and the related impact on the integrity and validity of the clinical data. The increased use of AI will continue this trend.

There have been a number of initiatives to develop clinical guidance on the use of AI in clinical trials, and in particular to improve the quality of evidence generated by AI. In particular, an international collaborative effort by academics, healthcare professionals, lawyers and others (called the SPIRIT-AI and CONSORT-AI Working Group), to improve the transparency and completeness of clinical trials evaluating interventions involving AI, has established:

- Standard Protocol Items: Recommendations for Interventional Trials - Artificial Intelligence (SPIRIT-AI).
- Consolidated Standards of Reporting Trials - Artificial Intelligence (CONSORT-AI).

SPIRIT-AI sets out guidance for clinical trial protocols, and CONSORT-AI sets out guidance for clinical trial reports, and they build upon existing recommendations to address considerations specific to AI health interventions (see The BMJ: Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI Extension (9 September 2020) and The BMJ: Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT_AI Extension (9 September 2020)). These are important guides for researchers as they seek to undertake clinical trials using AI technologies.

The medicinal products regulatory authorities have also published some guidance in this area. For example, the US Food and Drug Administration (FDA), the MHRA and Health Canada have developed "Ten International Guiding Principles on Good Machine Learning in Medical Devices", intended to "help promote safe, effective, and high quality medical devices that use artificial intelligence and machine learning (AI/ML)" (see GOV.UK: Good Machine Learning Practice for Medical Device Development: Guiding Principles (October 2021)). In

October, they also published "Predetermined Change Control Plans for Machine Learning-Enabled Medical Devices: Guiding Principles", which aim to remove the regulatory burden for developers of machine-learning-enabled medical devices, enabling reallocation of resources to improve product performance for patients (see GOV.UK: Predetermined Change Control Plans for Machine Learning-Enabled Medical Devices: Guiding Principles (24 October 2023)). See Legal update, MHRA and international partners publish guiding principles for machine-learning enabled medical devices.

In the EU, in July this year, the EMA published a draft reflection paper on the use of AI in the lifecycle of medicines (see European Medicines Agency: Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle (13 July 2023)) and Legal update, EMA publishes reflection paper on use of AI in the medicinal product lifecycle). The reflection paper recognises the value of this technology as part of the digital transformation within healthcare, and acknowledges its increasing use and potential to "support the acquisition, transformation, analysis, and interpretation of data within the medicinal product lifecycle", provided it is "used correctly". The EMA will take a risk-based approach to assessment, based on how the AI will be used and its functionality, and the greater the potential regulatory impact or risk, the greater the scrutiny from the EMA. As such, AI that is part of the decision-making process is likely to attract the highest scrutiny. In relation to clinical trials, the EMA notes that GCP guidance is expected to apply to AI systems used in clinical trials. Models generated for clinical purposes will be subject to comprehensive assessment during authorisation procedures and, where necessary, related information should be included in the protocol.

In the UK, in September 2021, the MHRA announced the Software and AI as a Medical Device Change Programme, that will review the regulatory environment applicable to medical software and AI in the UK (see GOV.UK: Software and AI as a Medical Device Change Programme (16 September 2021)). This announcement was followed in October 2022 by a Regulatory Roadmap, which sets out how the MHRA intends to regulate medical software and AI in the UK (see Legal update, MHRA publishes roadmap for regulation of medical software and AI in the UK). This confirmed that AI as a medical device will be regulated as a part of software as a medical device, with no additional legislative medical device requirements being imposed on AI beyond those for software. This is not specific to uses of AI in clinical trials, but the guidance the MHRA intends to generate is likely to include uses in this context.

Data protection issues

AI is inherently data driven and therefore raises data protection implications. This has prompted some data protection regulators to temporarily prohibit the use of certain AI tools and to issue updated guidance on how the technology can be used in a way that is compliant with data protection legislation. While not specific to clinical trials, certain aspects of the General Data Protection Regulation ((*EU) 2016/679*) (GDPR) (and the retained EU law version of the GDPR, the UK GDPR) are particularly relevant to AI software, such as the principle of transparency, which requires data controllers to provide comprehensive information to data subjects on all aspects of the processing of their personal data in a clear and understandable manner. This could be somewhat problematic in the context of complex AI models where it is not always clear exactly what the AI is doing or how. See Checklist, Complying with the UK GDPR's transparency requirements and Complying with the UK GDPR's transparency requirements toolkit. Another difficulty is compliance with the principle of accountability, which requires data controllers to prove they are GDPR (and UK GDPR) compliant. See Data protection accountability toolkit (UK).

Organisations are also required to implement security measures that are "appropriate to the risk" involved in the processing of the data. Uses in clinical trials inherently carry risk, and the nature and extent of that risk is not necessarily known at the beginning of the trial. The dual risk of clinical testing and the generative nature of AI is often difficult to address and requires communication with the authorities and ethics committees to ensure they are comfortable with the information being provided to patients. See Article, AI and privacy compliance: getting data protection impact assessments right and Practice note, Data ethics (UK).

Another issue is consent for the data processing elements, which is separate and in addition to the rules on consent for the clinical trial. Organisations often rely on individuals' consent under the GDPR and UK GDPR to legitimise the processing of personal data. However, the nature of AI techniques means that it can be difficult to obtain fully informed consent. Further, where there is automated decision making, which includes automated processing of personal data to evaluate a person and/or analyse or predict aspects of their health, the individuals must be informed explicitly of this both proactively (such as in the privacy notice) and reactively (in response to an access request). Individuals also have the right to object to automated decision making, which is difficult to manage during a clinical trial if the AI is an integral part of the protocol. See Practice note, UK GDPR and DPA 2018: profiling and automated decision-making.

Therefore, an alternative solution would be to rely on a different legal basis (such as legitimate interest, legal obligation, provision of healthcare, public interest in the area of healthcare or scientific research). In relation to this, the European Data Protection Board, the UK Health Research Authority (HRA) and the Information Commissioner's Office (ICO) in the UK expressed concerns about the use of consent as a legal basis for the processing of patients' personal data in the context of clinical trials and advised clinical trial sponsors to consider an alternative legal basis (see European Data Protection Board: Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection Regulation (GDPR) (23 January 2019), ICO: UK GDPR guidance and resources; What is valid consent? and NHS Digital: Data sharing standard 8 – GDPR Consent; as well as NHS Health Research Authority: GDPR guidance, Consent in research (19 April 2018)). This does not mean the AI issues are avoided, but should mean consent can be navigated more easily. See also Checklist, Data protection legitimate interests assessment (UK).

Safety monitoring

Safety is a key component of clinical trials. Whether the use of AI adds to the safety issues that are to be monitored during the trial will depend on the technology being used and its stage of development. As discussed above, the GCP requirements increasingly focus on data integrity, particularly in the context of use of electronic technologies and automation systems during the trial. These requirements will need to be considered carefully in the context of the operation of the AI technology in the trial to ensure the GCP requirements are met, and the sponsor can demonstrate they are met.

Safety of software used in a healthcare setting is scrutinised by regulators. As well as the clinical trial rules, there will be oversight under the MDR and the UK MDR, and in relation to UK GDPR and GDPR requirements on security issues that impact safety, and voluntary standards on security that impact safety. These issues are considered by the competent authorities in a similar way to vigilance data for devices and medicines. For example, the MHRA has investigated errors in machine learning software (specifically, a predictive algorithm) where the issue resulted in incorrect results being produced for a limited number of patients (see GOV.UK: MHRA information on TPP and QRISK®2 (9 June 2016)).

In May 2023, the MHRA published specific guidance on reporting adverse incidents involving Software as a Medical Device, which include AI (see GOV.UK: Guidance for manufacturers on reporting adverse incidents involving Software as a Medical Device under the vigilance system (15 May 2023)). As is the case for all medical devices, all adverse incidents where a manufacturer's device is suspected to be a contributory cause of an incident, and the event that occurred led, or might have led, to death or serious deterioration in health, must be reported to the MHRA as individual events, periodic summary reports or trend reports. In the case of AI, the guidance acknowledges some of the unique properties of software medical devices and the fact that for AI medical devices, the harm is likely to be indirect, such as incorrect or delayed diagnosis or inappropriate, delayed or no treatment. The understanding by the authorities should lead to a realistic view of which, and how, adverse events can be reported. In addition, the EU AI Act will require post-market monitoring as part of the risk management system for the AI, which will include similar provisions and will also need to be complied with once this Act has been finalised.

In a clinical trial, sponsors should have a clear plan, as part of the protocol, of what safety issues may arise, how these will be monitored and when they will be reported. This should take into account the particular features of the AI functionality and any specific requirements relevant to the AI itself when it is used as part of the trial. For example, the use of AI may have particular difficulties for monitoring the performance of the software, and being able to comply with vigilance obligations. If there is a machine learning element, this may mean that the device algorithm is constantly being updated. Vigilance systems (for the AI and the drug product) will need to adapt to such technologies, as acknowledged in the MHRA guidance, and additional guidance provided by the authorities as experiences increase.

Liability concerns

The use of a product during a clinical trial, which by definition encompasses an experimental environment where safety and efficacy are being explored, does not necessarily mean the product liability regimes do not apply. Across the EU, there are also no-fault schemes agreed with industry in certain member states in relation to harm caused during a clinical trial. The use of AI in such trials will need to be considered as part of these, and in particular whether the AI is also in development, or whether the AI is placed on the market as a commercial product and used as such in the clinical trial. This may cause complications for the liability of the AI technology and being able to identify which regime or compensation scheme should apply, and will need to be clearly addressed in the protocol and contractual arrangements between the parties. More broadly,

there has been little reported on how the courts are approaching questions of product liability in the context of new technologies such as AI, leading to uncertainty for companies.

However, in September 2022, the European Commission published a proposal for a new directive on liability of defective products and a new AI Liability Directive, with the aim of ensuring that victims benefit from the same standards of protection when harmed by AI products or services, as they would if harm was caused under any other circumstances (see European Commission: New liability rules on products and AI to protect consumers and foster innovation (28 September 2022)). For more information, see:

- Artificial intelligence toolkit.
- Legal update, European Commission proposal for a Directive on adapting non-contractual civil liability rules for AI (full update).
- Legal update, European Commission proposal for a revised Product Liability Directive (full update).
- Revised Product Liability Directive: legislation tracker.
- Artificial Intelligence Liability Directive: legislation tracker.

In the UK, the Office for Product Safety and Standards from the Centre for Strategy and Evaluation Services (CSES) commissioned a study that was published in May 2022 on the impact of artificial intelligence on product safety to examine the current and forecasted future impacts of artificial intelligence in consumer products, and what this means for product safety (see GOV.UK: Study on the impact of artificial intelligence on product safety (23 May 2022)). However, UK product liability laws have not been updated to specifically address the use of AI, and the general rules apply.