Artificial intelligence in clinical development and regulatory affairs – **preparing for the future**

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Keywords

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Abstract

Artificial Intelligence (AI) is set to transform healthcare product development with enormous potential to benefit patients, but also to other stakeholders including regulators and industry. This progress will present new challenges to the systems in place which regulate these products. Stakeholders must now work together to ensure the current regulatory systems evolve in time to embrace the future benefits of AI. This article reviews several areas where AI is being applied in healthcare product development which test current regulatory frameworks, or are topics that will need further consultation between industry and regulators to determine the optimal way to regulate these products in the future.

Introduction

This article is based on an Artificial Intelligence Consortium meeting held in Basel, Switzerland, on 16 April 2018, which discussed how health authorities and industry can join forces to foster the use of AI for accelerating clinical development and increasing the efficiency of regulatory processes. The Consortium consisted of health authority representatives, a non-government organisation (NGO) representative, and industry regulatory professionals.

AI is increasingly being applied in the pharmaceutical as well as medical devices industry and is expected to increase efficiency and the speed of product development and generate innovative solutions for improving and prolonging patients' lives. However, this progress applied to healthcare products will present new challenges to the systems in place which regulate these products. Stakeholders must now collaborate to ensure regulatory systems evolve to enable the adoption of benefits that AI should bring in the future.

There are a number of opportunities for use of AI in clinical development and during lifecycle management of healthcare products. The presented AI opportunities have been selected for article discussion as they use different AI technologies and cover different phases of development. In addition, they also provide a perspective for developing countries. For this review, the technologies explained in Table 1 are considered to be part of AI. In the context of this article, health authorities are considered to be those institutions which are reviewing the data and documents for an assessment of efficacy, safety and quality of new medicinal products and medical devices, eg, the US FDA and the European Medicines Agency (EMA) and national authorities such as the Dutch Medicines Evaluation Board or the Danish Medicines Agency.

Opportunities for the use of AI in clinical development and regulatory affairs

In the first part of this review, four selected case studies are presented to illustrate the potential of AI in product development and lifecycle management of healthcare products. The in-use cases are presented based on the sequence of their application in the lifecycle of a medicinal product starting in clinical development up to, and including, lifecycle management of a product.

- **Opportunity 1: Assessment of inclusion/exclusion criteria in clinical trials using AI tools.** AI may be utilised for the assessment of imaging or histopathology-related inclusion and exclusion criteria in clinical trials. Such applications of AI are expected because the first diagnostic tools using AI technologies have already entered the market.[1–3] With such tools it is anticipated that assessment of defined inclusion and exclusion criteria will become faster and at the same time less expensive with a higher degree of standardisation.

  Using AI tools can be particularly helpful when a disease needs to be diagnosed from biological samples such as blood or tissue. These samples can be assessed locally without the need to transport them across borders, which is usually a complicated and time-consuming process. This is particularly important for studies in low- to middle-income countries where there is commonly a lack of local experts to evaluate biological samples.
- **Opportunity 2: Use of AI for identification of clinical activity in Phase II clinical trials.** Using AI for assessment of clinical efficacy of new drugs carries the potential to reduce costs, accelerate clinical development and thus bring new therapies to patients earlier. One option for use of AI is the evaluation of imaging endpoints from CT scans or MRI scans in Phase II studies. AI-based algorithms can be applied to optimise reading and evaluation of imaging results, to reduce inter- and intra-reader variability and thus ultimately increase sensitivity and specificity of the measurements. It will also accelerate the outcome assessment and could reduce costs if the task no longer requires radiologists.

  Another option is the development of new clinical trial endpoints using AI algorithms to help reduce the number of

Table 1: Overview on AI technologies referenced in the text.

Technology	Description
Robotic process automation (RPA)	The application of technology that allows humans to configure computer software, aka "robots" ("bots"), to capture and interpret existing applications for processing a transaction, manipulating data, triggering responses and communicating with other digital systems.
Natural language processing (NLP)	Software that will analyse, understand, and generate languages that humans use naturally.
Machine learning (ML)	A field of AI, focused on getting machines to act without being programmed to do so. Machines "learn" from patterns they recognise and adjust their behaviour accordingly.

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required trial patients. For example, in patients with Parkinson's Disease, an accelerometer can be attached to a patient's wrist like a fitness tracker. This accelerometer will provide continuous data on the patients' motion disorder and its evolution over time. These data can be evaluated by AI algorithms to differentiate if a patient is in ON or OFF state and thus record whether a drug is active in modifying the disease progression. This assessment will considerably reduce variability as compared to using patient diaries or currently approved standards such as UPDRS-III scale where the exact times of ON and OFF state cannot be measured. If validated as an acceptable clinical endpoint, the reduced variability may facilitate recruitment of considerably fewer Phase II patients to identify a treatment effect of a new drug. Figure 1 illustrates the power of a clinical study in Parkinson's Disease plotted as a function of the sample size, either with or without continuous monitoring.[4] With the current UPDRS-III scale, more than 300 patients (150 patients per arm) are required to detect a slowing of the disease progression greater than 40% over 12 months when compared to the standard of care, eg, using patient diaries. With continuous monitoring using an accelerometer, it would be possible to achieve 80% power of a study with approximately 80 patients (40 patients per arm). This makes the conservative assumption that the variability of the endpoint is divided by four as compared to UPRS-III. Such a variance reduction is very likely since UPDRS-III scale is associated with extreme variability and can only be evaluated a few times, eg, four to six times, over a one-year period because it requires the patient to visit the hospital and to be off L-dopa for the evaluation. Having a continuous evaluation instead of staggered evaluations for detecting disease-modifying drugs should considerably boost the precision of evaluation and therefore individual trajectories of motor activity. This reduced sample size should make such a study less expensive and at the same time quicker to perform.

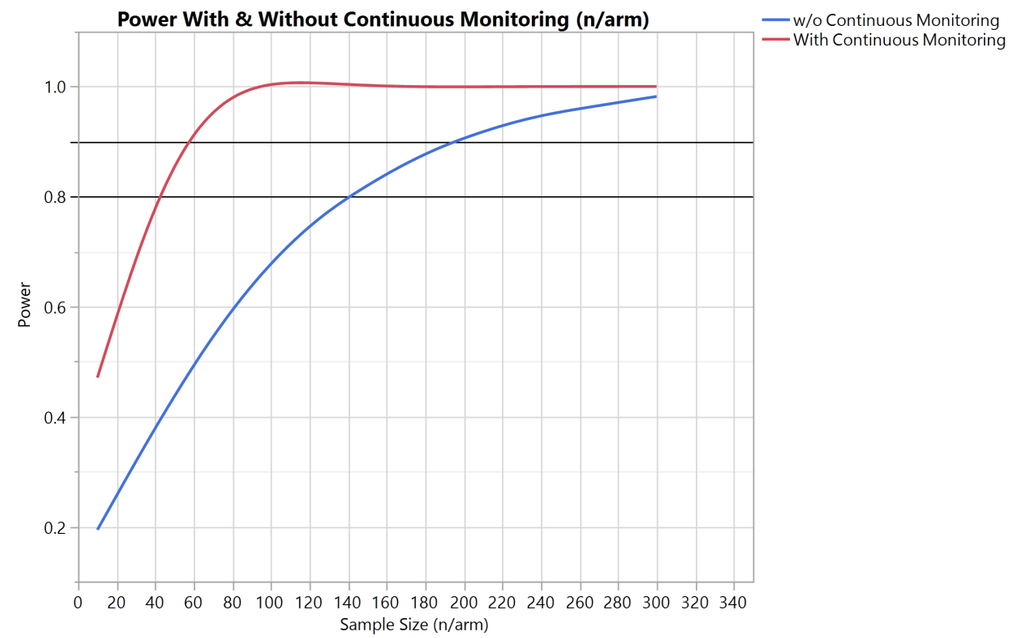
It is expected that the biggest impact of such technologic advances will be during Phase II clinical development, as Phase III clinical trials require a sufficient number of patients to appropriately assess the safety profile of a new product and validate the Phase II efficacy finding in a larger population. In addition, substantial validation is needed before any new clinical endpoint can be used routinely as a surrogate endpoint for demonstration of clinical benefit.[5]

- **Opportunity 3: Extraction of data from unstructured documents.** Valuable information is available in unstructured text documents at health authorities, healthcare companies, and also publicly on the internet. This includes rather complex information regarding regulatory intelligence but also more simple data, which could be easily evaluated once they are extracted and transferred to databases.

  New tools for text mining using natural language processing (NLP) offer novel possibilities for the extraction of information and data from documents and subsequent automatic upload into databases for analysis. AI-based tools are already available which allow extraction of data for identification of medicinal products (IDMP) such as substance name or strength from unstructured text documents such as a summary of product characteristics (SmPC) (see Figure 2).

  Using such text mining tools for chemistry manufacturing and control (CMC) documents and guidelines offers great potential for health authorities as well as pharmaceutical companies. Such tools will allow health authorities to evaluate documentation across different applications and marketing authorisations. Many beneficial examples can be thought of, like finding products which had the same chemical impurity in their manufacturing process. Another possibility is to look for a specific raw material used in the manufacturing of a new biological entity and to which extent it was removed during the manufacturing process. This will allow health authority reviewers to learn from precedence and improve decision making. For industry such tools offer the opportunity to automatically extract information from health authority guidelines and import it into regulatory intelligence systems. For both tasks NLP software is needed which is capable of understanding CMC documents. This software needs access to a significant amount of data to achieve results quickly, efficiently, and with high quality; therefore, joint health authority/industry initiatives could deliver the greatest benefit.
- **Opportunity 4: Automation of administrative work.** Health authorities and the healthcare industry manage vast amounts of administrative work that robotic process automation (RPA) and machine learning (ML) could help to reduce. For example, a review of the Regulatory Optimisation Group (ROG) has shown that around 400 full time equivalent (FTE) staff are employed across the authorities and industry to administer type IA variations in the EU.[6] At the AI Consortium meeting it was discussed how AI/

Figure 1: Impact on sample size by using continuous monitoring.



RPA can help automate the handling of type IA variations which a company can implement without authority approval, but the health authorities need to be informed within a specific timeframe about the change(s).

One application of AI in this context may be the intelligent extraction of information from scanned documents such as registration certificates or trade register copies and transfer of this information into databases using the 'SPOR' standard which includes substance, product, organisation and referential data (for details see Figure 3). Such technology is already in use for automatic processing of invoices where data given on an invoice are extracted into enterprise resource planning systems.

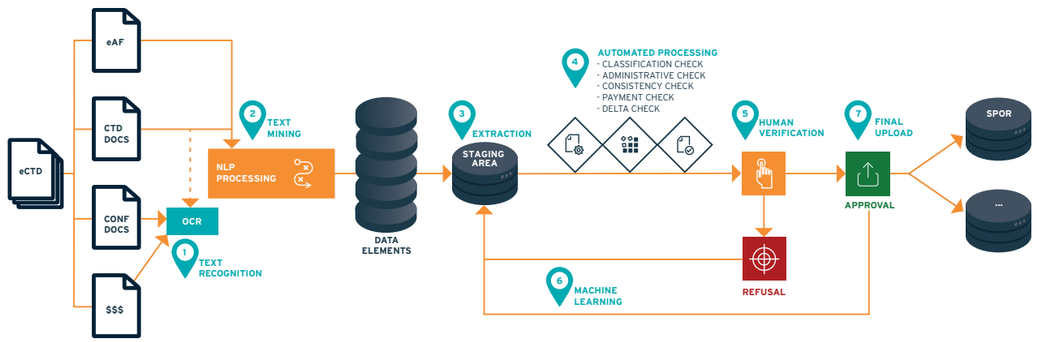
The use of AI in clinical development and regulatory affairs

There are regulatory challenges associated with the application of AI which are now discussed within this article.

Figure 2: Extraction of data from unstructured text in an SmPC using NLP.

Source: Averbis GmbH, Germany.

Figure 3: Flow chart on suggested automated workflow for type IA variations.



Note: Optical character recognition (OCR) transforms text and figures from a (scanned) image into machine readable data/text (1); CTD documents should already be in searchable PDF format, but confirmatory documents or proof of payments need OCR (2). Text mining transforms unstructured information from text documents into structured information/data by using NLP; this can be, for example, the address of an MAH or manufacturer, product or substance names or information such as dosage forms and routes of administration (3). The identified structured information ("snippets") is extracted and transferred into the staging area which holds structured information during the processing steps (4). Various consistency checks are performed as part of the automated processing (5). The system presents the results of the work flow and the consistency checks to a human processor; the human can correct potential mistakes and finally approve the dataset (6). The system improves its performance over time by learning from the corrections of the human processor (7). The identified structured information is transferred into the relevant database(s) using defined standards (eg, SPOR).

- **Challenge 1: How to validate AI-based software that is constantly "learning".** AI systems are constantly learning and hence they have vast potential for their use in the future of healthcare. This, however, raises an important question of how and when should AI-based software be validated when it continues to learn during use. One approach may be to validate it in a staggered fashion so that after a certain number of learning cycles it is re-validated. Another question concerns the aspect of whether to apply a risk-based approach for validation. This could be based on the hypothesis that the risks with systems which have completely autonomously learned to solve a problem are higher and therefore a more rigorous validation is required than for tools which just have been optimised using ML techniques. Furthermore, it seems reasonable to include a validation against "human raters" and final outcome. In any case, discussions are needed to define the most appropriate approach for validation of AI-based software.
- **Challenge 2: How to assess safety signals from new AI-based clinical endpoints.** As previously highlighted, AI-based technologies allow development of new endpoints for identification of clinical efficacy. However, such data may entail safety information that has to be thoroughly evaluated. In the prior example on continuous monitoring of patients using a wrist accelerometer, data may allow identification of a patient falling to the ground or a patient becoming inactive. Thus, when implementing such new methodology, due consideration must be given on how to capture and assess safety signals from these data.

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- **Challenge 3: How to organise the review of complex medical technologies which apply AI.** Increasingly complex medical devices/software, including those incorporating AI technology, are presenting regulatory authorities with progressively greater challenges to review. For example, recently the first AI software was approved that can identify disease without the need for a specialist[2] and additionally a neural network has been trained using deep learning techniques to diagnose melanoma from dermoscopic images.[7] Such products are reviewed and approved in the US by the FDA, while in the EU a medical devices certification system is in place. Therefore, the EU member states have designated 60 notified bodies (NBs) to determine conformance of medical devices/software with Directive 93/42/EEC. It is difficult for so many organisations to achieve and maintain the depth of knowledge necessary to regulate the increasingly complex technical products, especially when there is a high need to understand not only the technology but also the disease to which the device is applied. The AI Consortium meeting questioned assignment of complicated medical devices/software reviews to the EU health authorities and considered a centralised fashion to ensure that appropriate expertise is available for the assessment.

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- **Challenge 4: AI systems need data – who owns the patients' data?** AI systems need data to "learn" and in the context of many healthcare applications the data required will be from patients. The tools developed using these data are likely to provide benefits for future patient care, but are probably developed for commercial purposes and provide a return on their development investment. In this situation the question arises as to who owns the data and thus the subsequently developed tools. There is no simple answer to this question and the stakeholders such as patient groups, legal experts, healthcare providers, industry and hospitals need to closely cooperate and decide on a case-by-case basis depending on the project scope and the local and national compliance requirements.[8] To foster development of innovative AI-based tools using patient data, the implementation of an international framework with consistent requirements would be an advantage. Thus, discussions on this topic are clearly warranted and should also consider questions such as adequate data anonymisation.

Conclusions

Consensus across the regulatory professionals participating in the discussion was that AI offers numerous opportunities to improve healthcare in the future, with the potential to:

- Improve the robustness of data collected during clinical development
- Reduce the time and costs involved from discovery to market
- Reduce the workload for health authorities and industry
- Develop more innovative healthcare products.

To facilitate appropriate regulation of these advances we will need to further develop the existing regulatory frameworks by expanding the scope of current joint health authority/industry initiatives such as the International Conference on Harmonisation. ■

Disclaimer

The opinions expressed in this paper are the personal representations of the authors (Artificial Intelligence [AI] Consortium members) and do not reflect any endorsement or official status of their hiring organisations.

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