Artificial Intelligence in Clinical & Medical Research

Abstract

While clinical trials have become lengthy and very costly with low success rates, the application of innovative artificial intelligence (AI)-based approaches has been recognised for its potential to transform the slow and expensive current approach to clinical trials into a more cost-effective process with higher success rates. Over the past few years, the number of AI-based approaches are being increasingly applied across different stages of drug development such as drug discovery, manufacturing, clinical trial data management, and pharmacovigilance, which have already increased the biopharmaceutical industry's ability to improve the drug development process. The adoption of these AI-based approaches is steadily increasing within biopharmaceutical companies, are also now often partnering with a variety of companies developing AI-based approaches. This positive trend in adopting this technology is partially due to a new regulatory frameworks established by regulatory agencies combined with a growing culture of data sharing and data digitisation, which are incentivising biopharmaceutical companies to reshape critical steps of the drug development process and and using AI-based approaches. In the next few years, remarkable advancements and stunning efficiencies in drug development as well as significant patient-centric applications could be gained by implementing novel AI-based approaches.

Introduction

Rapidly increasing amounts of clinical data available to the biopharmaceutical industry has enhanced the allocation of resources by many established and start-up companies to develop and use novel AI-based approaches. The biopharmaceutical industry is gaining understanding of the power of large-scale data management and analysis by leveraging these AI-based approaches. It is becoming increasingly evident that AI-based approaches can add value across the spectrum of clinical trials, including protocol development, drug regimen selection, clinical site selection, and participant management. Biopharmaceutical companies can now better understand their own data repositories and how they can leverage insights more effectively for future clinical trials using AI-based approaches, which translates into a better use of data, and a higher return on investment (ROI) over time. These AI-based approaches have the potential to improve clinical trials success rates, and therefore bring new treatments to patients sooner. In addition, there is an unparalleled opportunity to adopt a wide range of patient-centered AI-based approaches to reduce the burden on participants in clinical trials. In this editorial, we will describe novel AI-based approaches that are currently being developed and implemented in clinical trials, provide regulatory considerations, and make some final remarks on the near future of AI-driven clinical trials.

Novel AI-based Approaches to Clinical Trials

Participant selection, recruiting, and retention constitutes the number one cause for clinical trial delays and are key factors causing a clinical trial to be unsuccessful; 86% of all clinical trials do not meet enrolment timelines and close to one third of all Phase 3 clinical trials fail due to enrollment issues.[1]

Improving participant selection is critical in a clinical trial design because it may decrease the number of participants required to observe a treatment effect – by increasing the likelihood of a participant to respond to the study drug – which has important ramifications, including reducing clinical trial costs and time burden for biopharmaceutical companies and clinical research organisations (CROs). The other side of the coin is that it may decrease the number of participants exposed to treatments from which they are not likely to obtain benefit. This is not trivial, as it has been reported that the ten-highest grossing drugs in the United States (US) fail to improve the conditions of many individuals,[2] i.e., there are effective treatments for a few and ineffective treatments for many. While improving participant selection does not guarantee success of a clinical trial, enrolling unsuitable participants increases the likelihood of its failure. There are multiple AI-based approaches that can facilitate more efficient participant identification for a clinical trial. Some AI-based approaches have the ability to correlate large and diverse datasets such as electronic health records (EHRs), medical literature, and clinical trial databases to improve participant-trial matching. Another AI-based approach is changing the traditional approach to drug development; instead of aiming to find the proper treatment for a given disease, it finds the suitable participant for a given treatment by predicting a participant's clinical progression across a specific disease.

Improving participant retention during a clinical trial may be critical to demonstrate the efficacy of a study drug. A large number of participants who drop out during a clinical trial may lead to an underpowered clinical trial, which negatively impacts the clinical trial data and the integrity of the clinical trial. Novel AI-based approaches can reduce the clinical trial burden for participants in a variety of ways, and therefore improve participant retention. There are some AI-based approaches that enable capturing participant data outside of the context of a clinical trial, which reduces the burden of data collection for participants. Another AI-based approach is to directly target the participant's sentiment using semantic tagging and linguistic parsing; this technology can identify participants who are at risk of dropping out and recognise what factors lead participants to consider leaving the clinical trial. Other AI-based approaches have developed ways to analyse conversations between participants and Principal Investigators (PIs)/site staff to improve the participant engagement process; methods have also been developed to capture remote data through sensor-equipped wearable devices and other remote data-capture technologies that enhance the understanding of participants' behaviour during a clinical trial. In addition, there are AI-based approaches that can enable participant monitoring

and gathering of real-time insights by automating data collection, digitalising common clinical assessments, and sharing data across systems, thereby predicting the risk of participants likely to drop out. An AI-based mobile application using facial recognition aimed to measure study drug adherence during a clinical trial has shown to increase compliance by 25% in a Phase 2 clinical trial.[3]

Proper clinical site identification is one major step in setting up a clinical trial to successfully recruit the required number of participants without incurring costly recruitment delays. The process of selecting clinical sites for a clinical trial typically includes factors such as participant population availability, resources, and data collection procedures at the clinical site. However, the lack of transparency in clinical site quality combined with personal relationships and level of confidence with PIs may create bias in the selection process within biopharmaceutical companies/CROs. AI-based approaches can help to resolve these issues. For example, applying the inclusion and exclusion criteria of a particular clinical trial through an AI-based algorithm to the clinical site database can enable biopharmaceutical companies/CROs to determine a more precise and realistic number of participants available for recruitment at a clinical site for a specific clinical trial. Another unbiased AI-based approach expedites clinical trial start-up and successfully predicts recruitment, identifying high-performing clinical sites and qualified PIs by leveraging mathematical modelling based on past clinical site performance.

Poor selection of clinical sites is closely associated with the particularities of each clinical trial protocol. Specific modifications in inclusion and exclusion criteria, endpoints, and particular requirements for each clinical trial may lead to higher levels of screen failures at a given clinical site than anticipated. This is just one reason, among others such as protocol design inconsistencies, regulatory requests, and participant recruitment difficulties, that typically leads to protocol amendments. Protocol amendments can lead to months of delays and adds hundreds of thousands of dollars to the cost of a clinical trial. According to the Tufts Center for the Study of Drug Development (Tufts CSDD), almost 60% of clinical trial protocols are subject to amendments.[4] AI-based approaches can de-risk protocol amendments due to the capability to mine large amounts of clinical trial-related documents needed to develop a protocol and attain it faster and on a larger scale. For example, an AI-based platform enables faster and more efficient protocols by recommending the optimal primary and secondary endpoints to ensure they are acceptable to regulators, payers, and participants. The platform can also determine how the eligibility criteria impacts outcomes such as cost, study duration, or participant retention.

As the biopharmaceutical industry keeps developing and implementing new AI-based approaches, we can also learn from other industries that excel at adopting novel technologies. For example, adopting novel AI-based approaches such as digital twins – a digital representation that allows modelling the state of a real-world person or process; this technology has been applied to aircraft engineering and spacecraft simulators and is considered to have impressive potential in revolutionising the field of health.[5] In the healthcare space, we find start-ups aiming to shorten the time-to-market for medical devices by creating digital twins of bone and muscle groups to simulate how medical devices or implants might degrade within a patient's body over time, or creating digital twins focused on metabolism, which individuals and their providers use to plan out lifestyle changes that could help prevent or reverse metabolic disease. Digital twins are the latest technology that biopharmaceutical companies are exploring to transform drug development. Digital twins can be used, for example, to test new drugs to ascertain drug safety and effectiveness. Also, predicted clinical outcomes from digital twins generated from participants' baseline data in randomised clinical trials (RCTs) can enable clinical trial designs with fewer required number of participants or higher power without introducing bias and generating reliable evidence similar to traditional RCTs.

Regulatory Considerations

Regulatory agencies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) play a critical role in endorsing the use of AI-based approaches in clinical trials and importantly, accepting these approaches as part of a new drug marketing application package. Regulatory agencies have at least two important roles in this context.[1] Serving as active reviewers of AI-based evidence to gain internal confidence in the outcomes. As data sharing becomes recognised as increasingly valuable among regulatory agencies and biopharmaceutical companies, it incentivises the development and implementation of AI-based approaches in clinical trials. This trend should facilitate reproducibility and data validity, which will gradually "move the needle" of the regulatory agencies' confidence in the safety and effectiveness of this technology in clinical trials.[2] Serving as a catalyst of change, working closely with the biopharmaceutical industry to continue expanding regulatory frameworks for assessing AI-based approaches.

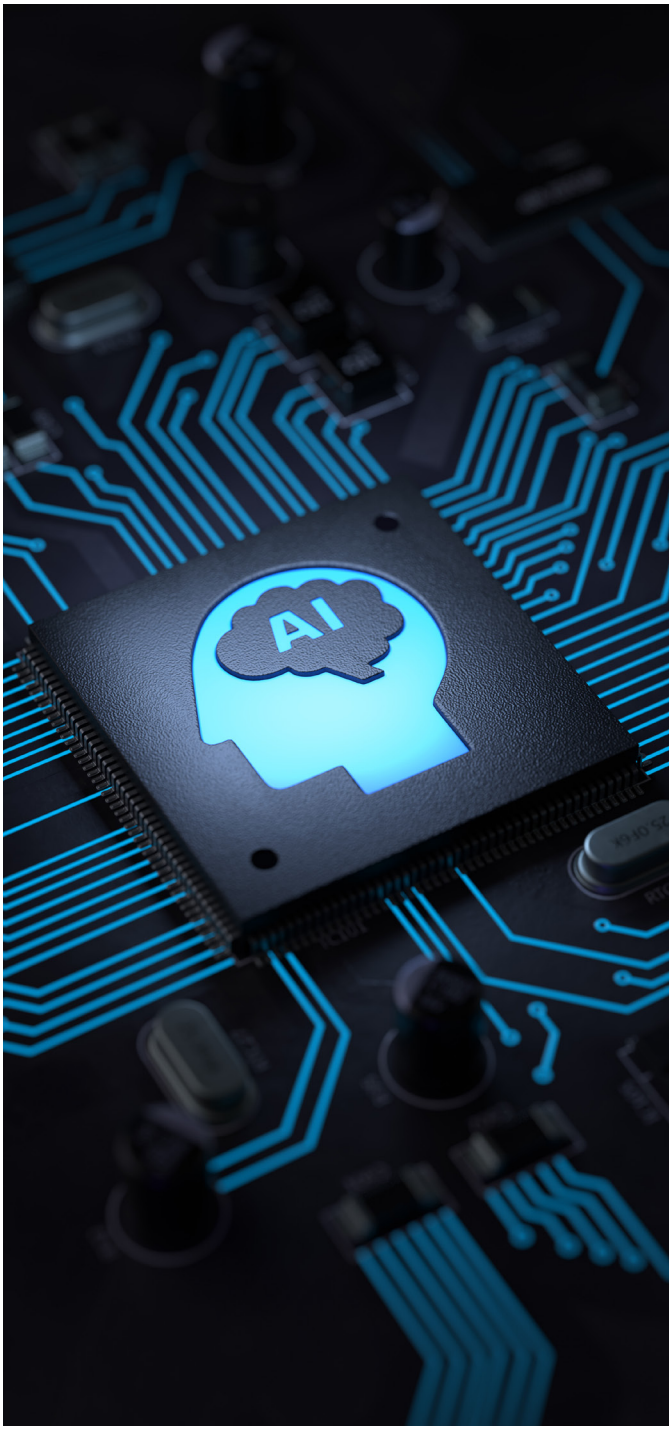
Currently, the FDA largely regulates AI-based approaches as Software as a Medical Device (SaMD). Approved SaMD includes software that helps to detect and diagnose a stroke by analysing magnetic resonance imaging (MRI) images, or computer-aided detection software that processes images to aid in detecting breast cancer. In addition, the FDA has recently expanded its established qualification programs for drug development tools (DDTs) – biomarkers, clinical outcomes assessments, and animal models – to include the Innovative Science and Technology Approaches for New Drugs (ISTAND). ISTAND is a pilot program to encourage the development of DDTs that are out of scope for the existing DDT program such as AI-based approaches. On the other hand, EMA has well-defined regulatory pathways to qualify novel technologies such as AI-based approaches - the qualification of novel methodologies for medicine development. Recently, the International Coalition of Medicines Regulatory Authorities (ICMRA), a strategic coordinating, advocacy, and leadership entity of regulatory authorities that work collaboratively, has made recommendations to help regulators address the challenges that the use of AI poses for global medicines regulations.[6] Some of these recommendations include the need to apply a risk-based approach to assessing and regulating AI, or establishing strengthened governance structures within biopharmaceutical companies and developers of AI-based approaches to oversee algorithms and AI deployments that are closely linked to the benefit/risk of a medicinal product. In addition, there are legal frameworks such as the US Health Insurance Portability and Accountability Act (HIPAA) and the European Union General Data Protection Regulation (GDPR); these statutes and regulations continue to evolve as governing and protecting sensitive health data becomes increasingly complex.

AI and Future Clinical Trials

In future years, clinical trials are expected to become increasingly decentralised, customised, and built on precise predictions of clinical trial outcomes, which will lessen the financial and time burden on participants. Connected AI-enhanced digital technologies will substantially transform clinical trials by making them safer, more efficient and effective, and above all, truly patient-centric, i.e., making decisions based on participants' needs and perspectives. While it is evident that there is huge potential for AI-based approaches to transform clinical trials, we cannot avoid the ethical and legal challenges that these AI-based approaches pose. Challenges such

as including the appropriate description of this technology into the informed consent, safety and transparency, algorithmic fairness and biases, data protection and privacy, or safety and effectiveness need to be carefully considered as we incorporate these technologies. In addition, widespread implementation of AI-based approaches within the biopharmaceutical industry will not happen overnight, as this industry has a long-standing tradition of risk-aversion. Barriers such as the reluctance to incorporate new technologies in an industry with an already high risk of failure, the difficulty in definitively quantifying benefits like patient-centricity and the overall probability of success will need to be overcome.

Years from now, when we look back at today's breadth of AI-based approaches, we will likely determine that we were only seeing the tip of the iceberg for the potential uses of AI-based approaches in drug development. The AI space is experiencing huge momentum in drug development and adoption of these technologies seems to be within a matter of time despite predictable resistance. A recent market forecast for the global AI use in drug discovery and development is estimating a Compound Annual Growth Rate (CAGR) of 31.6% from 2020 to 2027, with a market valued at $520 million in 2019, and projected to reach $4,815 million by 2027.[7] These AI-based approaches will continue to bring greater precision and efficiency to each stage of the process by, for example, leveraging more data from each participant, developing novel participant-centric endpoints, and collecting and analysing real-world data. Importantly, evaluation of successful implementation of AI-based approaches over time will be warranted and key performance indicators such as clinical trial success rates, average time to conduct a clinical trial, participant safety, and reduced participant burden should be taken into account. It is our collective responsibility to embrace the opportunity that AI-based approaches present to make clinical trials significantly more efficient and more patient-centric. To quote the former CEO of the Walt Disney Company Bob Iger, "the riskiest thing we can do is just maintain the status quo."



REFERENCES

1. Huang, GD, Bull J, Johnston, K et al., 2018. Clinical trials recruitment planning: A proposed framework from the Clinical Trials Transformative Initiative. Contemporary Clinical Trials; 66 (74-79)
2. Schork, NJ. 2015. Personalized medicine: Time for one-person trials. Nature; 520 (609-611)
3. Bain, EE, Shafner, L, Walling DP, et al., 2017. Use of a novel artificial intelligence platform on mobile devices to assess dosing compliance in a Phase 2 clinical trial in subjects with schizophrenia. JMIR Mhealth Uhealth; 5(2): e18
4. Getz, KA, Stergiopoulos, S, Short, M et al., 2016. The impact of protocol amendments on clinical trial performance and cost. Therapeutic Innovation & Regulatory Science: 50 (436-441)
5. Erol, T, Mendi AF, Dogan, D. 2020. The Digital twin Revolution in Healthcare. 4th International Symposium on Multidisciplinary Studies and Innovative Technologies (ISMSIT).
6. https://www.ema.europa.eu/en/news/artificial-intelligence-medicine-regulation
7. Allied Market Research. Artificial Intelligence for Drug Development and Discovery Market By Type, Indication, and End User: Opportunity Analysis and Industry Forecast, 2020-2027

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