Artificial intelligence in managing clinical trial design and conduct: Man and machine still on the learning curve?

Artificial intelligence (AI), first described in 1955, is the science and engineering of making intelligent computer programs.[1] AI can be described as "an entity (or collective set of cooperative entities), able to receive inputs from the environment, interpret and learn from such inputs, and exhibit related and flexible behaviors and actions that help the entity achieve a particular goal or objective over a period of time."[2] The ultimate goal of AI is to use machine simulation of human intelligence processes such as learning, reasoning, and self-correction, to mimic human decision process.[3] AI is fast emerging as an omnipotent solution for diverse health-care management problems. Worldwide spending for AI is expected to grow to $52.2 billion in 2021.[4] Pharmaceutical research and discovery, the second fasted growing discipline, was estimated to grow at 70.5% CAGR between 2016 to 2021.[4]

AI encompasses a variety of techniques: machine learning (ML), deep learning (DL), natural language processing (NLP), and optical character recognition (OCR). ML, widely used in pharma industry, creates data analytical algorithms and mathematical models to extract features from sample data, with the objective of making predictions or decisions.[3,5] ML is divided into (1) unsupervised learning applied for data extraction and (2) supervised learning employed for predictive modeling.[5] DL is a class of ML methods based on artificial neural networks that use multiple hidden layers to progressively extract and handle complex data from raw input.[3,5] NLP, another area applied to drug development, is utilized to extract meaning from textual information or natural language data.[3,5] OCR utilizes pattern recognition, and computational vision, with the objective of electronically converting images of typed, handwritten, or printed text into machine-encoded text.[3]

ML-based applications are utilized in diverse health-care domains – early disease prediction, diagnosis, and treatment, outcome prediction and prognosis evaluation,[5] personalized treatments, behavior modification, drug discovery, manufacturing, clinical trial research, radiology and radiotherapy, smart electronic health records, and epidemic outbreak prediction.[6] Although AI had potential utility in the COVID-19 pandemic for tracking and prediction, diagnosis and prognosis, treatments and vaccines, and social control, its value was limited by lack of data, and too much data, and by constraints of data privacy.[7]

In this issue of the journal, Karekar *et al.* have reported on 159 AI studies registered in Clinicaltrials.Gov.[8] The most common studies were in oncology, cardiology, ophthalmology, psychiatry, and neurology. Majority studies were for devices and diagnostics. Although this was an audit of registered studies, the authors have not discussed the quality of studies. Liu *et al.*, in a recent systematic review and meta-analysis of more than 30,000 AI-based diagnostic studies, found that diagnostic performance of DL models was equivalent to that of health-care professionals.[9] However, <1% of studies had sufficiently high-quality design and reporting to be included in the meta-analysis.[9] Recent guidelines – SPIRIT-AI Extension and CONSORT-AI Extension – are expected to promote transparency and completeness for clinical trial protocols for AI.[10,11]

For pharma industry, AI is becoming a versatile tool, which can be applied in all stages of drug development, such as identification and validation of drug targets, designing new molecules, repurposing of old drugs, improving efficiency of clinical trial conduct, and pharmacovigilance (PV).[3,12,13] AI is specifically tried in clinical drug development, which is plagued by high costs and high failure rates. DL has exhibited remarkable success in identifying potential new drug candidates and improving prediction of their properties and the possible safety risks.[12] AI can improve the efficiency of search for correlation between indications and biomarkers and help in selecting lead compounds which could have a higher chance of success during clinical development.[3] DSP-1181, a molecule for obsessive–compulsive disorder, created using AI, has entered a Phase I trial.[14]

AI offers the promise of transforming crucial steps of clinical trial conduct-study design, planning, and execution.[3] ML, DL, NLP, and OCR can be used for linking big and diverse datasets such as electronic medical records (EMRs), published medical literature, and clinical

trial databases to improve recruitment by matching patient characteristics to selection criteria.

AI can help in enhancing patient selection by:

1. Reducing population heterogeneity. This could be done by harmonization of large EMR data from diverse formats and different levels of accuracy and by leveraging electronic phenotyping[3]
2. By prognostic enrichment – selecting patients who have a higher probability of having a measurable clinical endpoint. ML techniques, using key biomarkers of Alzheimer's disease (AD), are deployed for prognostic enrichment[3]
3. By predictive enrichment – choosing a population with a better likelihood of responding to a treatment. For early AD, a clinical trial simulation tool developed by modeling drug, disease, and progression of disease, which helped in predictive enrichment, has undergone regulatory review.[3]

AI systems can be utilized for automatic analysis of EMR and clinical trial digital eligibility databases and match these with recruiting clinical trials from trial announcement, social media, or registries.[3] It can also help patients become aware of clinical trials of interest sooner and allow them to approach investigator sites for evaluation of eligibility.[3] AI-based clinical trial matching has facilitated an increase in enrollment in a lung cancer trial by 58.4%.[15]

AI techniques, in combination with wearable technology, are valuable in efficient, real-time, and personalized monitoring of patients automatically and continuously during the trial. This can improve compliance with protocol requirements and reliability of assessment of endpoints.[3] DL models, by analyzing data from wearable sensors and video monitoring, can generate patient-specific disease diaries adapted to behavioral changes and disease expression. Such dynamic disease diaries facilitate efficient and reliable collection of compliance and endpoints. ML technologies, approved for detection of medical images, would play an important role in image-based endpoint detection.[3] ML-based algorithms have been tried to determine the smallest and fewest doses required to shrink brain tumor, while reducing chemotherapy adverse effects, in simulated trials.[16] This could reduce the risk of dropouts due to safety issues.

AiCure, an AI-based mobile application to measure medication adherence, increased compliance by 25% in a Phase II trial of schizophrenia, compared to conventional modified directly observed therapy.[12]

AI-assisted patient-monitoring systems, employing images and videos from wearable sensors, have been recently tested. Wearable device is a device which can perform a measurement or data-processing activity, and which is fully functional while attached to the human body directly or indirectly through clothing, but which does not have a hardwired connection to any other nonwearable device.[3] ML models, coupled with wearable devices, have been applied in automatic detection of cognitive and emotional states, in monitoring participants in Parkinson's disease trials, and in assessing quality of sleep in neurology trials.[3] ML, NLP, and OCR could help in analyzing unstructured medical records in paper format for real-world evidence studies in Indian setting.

ML and NLP have been used to automatically detect adverse events and drug–drug interactions. Cognitive services, a combination of ML and NLP algorithms, have been identified and developed to solve specific tasks in the PV process of Individual Case Safety Reports, which would require human intelligence.[17] Such AI techniques can reduce the cognitive burden of PV professionals and improve efficiencies of various PV processes.

Despite rapid advances in AI technologies for clinical drug development, implementation of AI is facing a variety of challenges.[3,13] Major hurdles for EMR data mining are accessibility, digitization, and data integrity. Harmonization, interoperability of diverse formats, and standardization are common issues for all technologies such as EMR and wearable devices. Difficulties of mining large data sets of genomic data, past clinical studies, journal articles, and related real-world data, potentially distributed across multiple institutions and geographies, appear herculean.

Regulatory environment on data privacy restricts access to individual patient data. Similar legal barriers of data privacy and security impact clinical trial matching process.

The Food and Drug Administration (FDA) considers AI/ML-based software as a medical device.[1] FDA would expect the AI innovators to comply with requirements of clinical, analytical, and technical validation, quality systems, good machine learning practice, assurance of safety and effectiveness, transparency, and real-world performance monitoring. Any new AI technology, which proposes to improve the efficiency of clinical trial design and conduct, should be validated by testing alongside the existing technology it claims to complement or substitute.[3]

The regulatory agencies and the end users would expect that AI technology should be understandable, ethical, replicable, and scalable.[3] Finally, there are also personnel issues such

as availability of personnel with requisite technical skills[13] and fear of job loss which may delay the adoption of AI technology.

AI is not a quick fix panacea which can improve efficiencies of clinical trials overnight. Man and machine are still on the learning curve! Hence, pharma industry will have to invest substantial effort, money, and time – 5–8 years to realize the benefits of novel AI tools.

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