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Review Article

ROLE OF ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN CLINICAL TRIALS

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ABSTRACT

Clinical trials are conducted in order to find novel therapies, interventions, or tests to prevent, detect, treat, or manage a variety of illnesses or medical problems. AI is primarily concerned with robots aiding surgeons. It aids in the reduction of medical errors, digital acquisition, algorithm correction, scientific literature reading, and electronic record keeping. AI plays a vital role in clinical trials, By employing machines to handle enormous and massive data sets. Clinical trials might benefit from machine learning to increase their effectiveness, generalizability, patient-centeredness, and efficiency. Machine learning may help with preclinical drug development, pre-trial planning, data management and analysis in clinical trials. In this review we discuss the role of artificial intelligence and machine learning in various domains of clinical trials such as patient selection, study design, Pharmacovigilance, clinical monitoring, clinical data management, safety signals, data analysis etc. This article gives the overview of remarkable role of artificial intelligence and machine learning in clinical trials.

KEYWORDS: Clinical trials, Artificial intelligence, Machine learning, clinical study, data, patient.

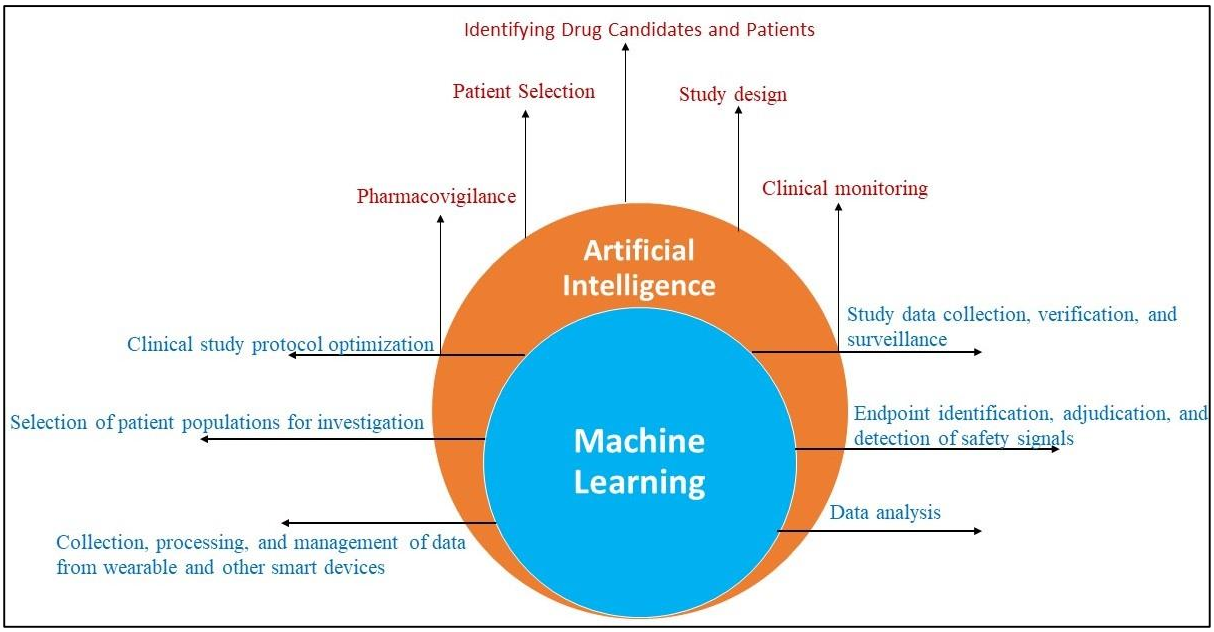

Figure no. 1 Graphical Abstract

INTRODUCTION:

Clinical trials, as the name implies, are a series of tests and observations carried out in human participants for the purpose of clinical research. They are conducted in order to find novel therapies, interventions, or tests to prevent, detect, treat, or manage a variety of illnesses or medical problems. Clinical trials aid in assessing if a novel intervention is effective, safe, and effective, as well as whether it is superior to already existing therapies. According to WHO, a clinical study is defined as: 'Any research study in which human participants or groups of individuals are randomly assigned to one or more health-related treatments in order to assess the effects on health outcomes. 'The primary goal of drug discovery research is to develop newer, safer, and more effective medications for human use. Before a new medicine can be put on the market, it must go through a series of rigorous testing procedures, first in animals and then in people. They are the most crucial and deciding factor in the introduction of a new medicine to the market. Researchers cannot correctly assess if novel medications produced in the laboratory or using animal models are useful or safe in a clinical context without clinical trials. They also cannot tell whether a diagnostic test works properly in a clinical setting without clinical trials.

The major purpose of health-related artificial intelligence (AI) applications is to discover connections between preventative or treatment methods and patient outcomes. AI is a word used to describe a simulation of human intelligence instilled in computers that are built to think like humans. The term is also used to describe any machine that demonstrates some features associated with human mental processes such as learning and problem-solving. The application of AI for diagnosis decision assistance dates back to the 1970s. However, once constructed, they were stiff and difficult to change.**[1]** Patients, physicians, and hospital administrators' life are made easier by AI, which performs activities normally performed by humans in a fraction of the time and at a fraction of the expense. Large caseloads and data, as well as incomplete medical histories, can lead to fatal human mistakes. As a result, AI can identify and forecast disease faster than most

medical practitioners.[2] In medicine, there are two forms of AI: virtual and physical. The virtual side of AI includes anything from electronic health record-keeping systems to neural network-based medical decision-making help. The physical side of AI is primarily concerned with robots aiding surgeons, producing intelligent prosthetics for the disabled, and geriatric care.[3] The foundation of evidence-based medicine is to build specific clinical correlations while creating linkages and patterns from the database's current understanding. Statistical tools have traditionally been used to establish these patterns and relationships. Flowcharts and database approaches are the two primary methodologies used to teach computers how to diagnose a patient.[4] The flowchart-based technique entails translating the process of history-taking, in which a physician would ask a series of questions before integrating the symptoms reported to arrive at a likely diagnosis. Given the vast diversity of symptoms and disease processes encountered in everyday medical practise, this necessitates sending a huge volume of data into machine-based cloud networks. Because the computers will not be able to see and diagnose cues that can only be observed by a doctor during the patient contact, the consequences of this technique will be restricted. However, AI aids in the reduction of medical errors, digital acquisition, algorithm correction, scientific literature reading, and electronic record keeping. By employing machines to handle enormous and massive data sets, AI plays a vital role in medical practise, thanks to its ultra-fast computing rates. While diagnostic abilities are useful, they are restricted to the computing infrastructure.[5]

Over the last ten years, interest in machine learning (ML) for healthcare has exploded. Though machine learning has been an academic field since the mid-twentieth century, advances in computer capabilities, data availability, innovative approaches, and a growing pool of technical talent have hastened the application of machine learning to healthcare. The academic and general press have focused most of their attention on applications of machine learning in healthcare delivery; however, uses of machine learning in clinical research are less commonly highlighted. Clinical trials might benefit from machine learning to increase their effectiveness, generalizability, patient-centeredness, and efficiency. ML techniques for handling massive and heterogeneous data sources, detecting complicated and hidden patterns, and forecasting complex outcomes are also accessible. As a result, machine learning may help with anything from preclinical drug development to pre-trial planning to data management and analysis in clinical trials. Despite the paucity of academic and lay publications on ML-enabled clinical research, the abundance of established and start-up companies devoting significant resources to the field indicates a high level of interest in, and burgeoning attempts to apply ML to clinical research, particularly clinical trials.[6]

Artificial Intelligenece:

Building theories and models of (appropriately embodied) brains and minds, both natural and artificial, is part of the effort to explain intelligence. This has been a key topic in philosophy since the earliest writings of India and Greece. With the introduction of the digital computer in the 1950s, this became a major worry for computer scientists. The parallel development of computation theory (by John von Neumann, Alan Turing, Emil Post, Alonzo Church, Stephen Kleene, Markov, and others) provided a new set of tools with which to

approach this problem, through the analysis, design, and evaluation of computers and programmers that exhibit aspects of intelligent behavior, such as the ability to recognize and classify patterns, reason from premises to logical conclusions, and learn from experience.

The phrase "artificial intelligence" refers to the process of learning about and creating intelligent systems. During the workshop at Dartmouth in 1956, where the field took on its modern incarnation, John McCarthy (who, incidentally, made several major contributions to AI and Computer Science in their infancy by designing the programming language LISP and the first time-sharing operating system) is credited with coining the term.

Here are some AI definitions:

1. Artificial intelligence (AI) is a branch of intelligence research. AI is primarily concerned with falsifiable statements, or testable hypotheses about the structures and processes that are required and sufficient for intelligent action.
2. The study of computational models of intelligent behavior - perception, cognition, and action is known as artificial intelligence (AI)
3. AI is the study of the universe of potential and existent intelligent systems.
4. AI is the business of creating and analyzing intelligent agents.

Proving theorems, planning trips, recognizing faces, diagnosing diseases, designing computers, composing music, discovering scientific laws, proving mathematical theorems, playing chess, writing stories, teaching physics, negotiating contracts, and providing legal advice are all examples of tasks that are thought to require intelligence when performed by humans. All excellent engineering, on the other hand, is built on a strong scientific foundation. AI is no different.[7]

The human mind's fundamental restriction in acquiring enormous volumes of info is essentially time limits. The learning process necessitates the integration of information and experience gained through time. Large volumes of patient data may be accessible, recorded, and stored for processing in the era of silicone chips. The cornerstone of AI is harnessing these massive data banks and changing them to acquire experience.[8] Through the use of algorithms, computer software may gather substantially more expertise in a much shorter period of time than human beings can in a lifetime. A radiologist will examine at around 225,000 MRI/CT tests over the course of a 40-year career, but AI can start with this amount and quickly scale up to millions of scans, significantly enhancing its accuracy. As a result, the accuracy and speed with which CTs are interpreted and diagnosed by AI should be far superior to that of a person.[9] Artificial intelligence (AI) is the capacity of a machine to emulate intelligent human behaviour in general, however it is not fully defined. While this broad phrase spans a wide range of computer scientific disciplines, in medicine, the following terms should be considered:

1. Image processing: A mathematical procedure that improves the clarity, retrieval of specific information, or pattern measures of a picture. The input is essentially an image, and the output is a more defined picture for a certain use.[10]
2. Computer vision: Image processing that allows for the identification of the picture input and the generation of a suitable output, i.e. image interpretation.[10]
3. Artificial neural network (ANN): The input is entered into a series of algorithms, and the output is re-entered into a new set of accommodation alters. This method uses neural networks to mimic the human brain's processing of various sorts of input and the creation of patterns for use in decision-making.[10]
4. Convolutional neural network (CNN): a form of artificial neural network (ANN) that analyses data using deep learning methods with numerous hidden layers. The interactions between layers are complicated (hence the word convolutional), and each CNN has many hidden layers.[10]
5. Deep learning: Deep learning is a subset of machine learning that is structured similarly to human brain processing, taking into consideration several input sets at once, evaluating and reprocessing for second and third distinct assessments, and so on, until an output is reached.[10]

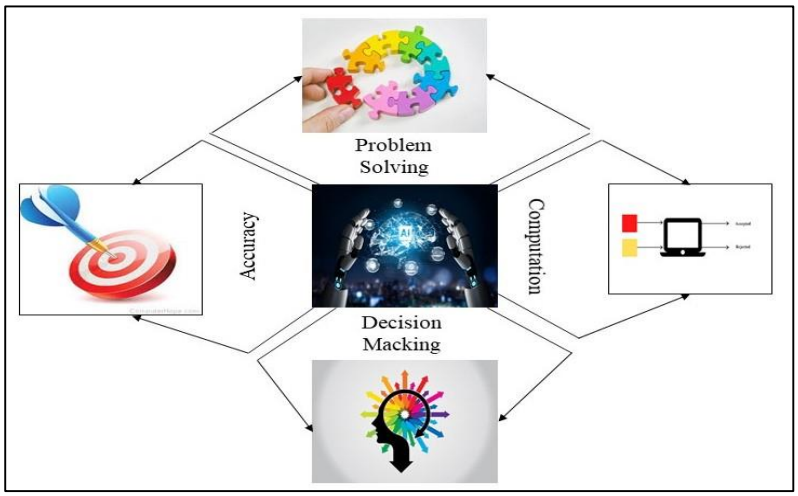

Figure no. 2 Characteristics of Artificial Intelligence

Role of Artificial Intelligence in Clinical Trials:

Patient Selection:

Every clinical study has its own set of eligibility, appropriateness, motivation, and empowerment requirements for patients who want to participate. A patient's medical history may make them ineligible for treatment. An eligible patient may not be at the stage of disease or belong to a certain sub-phenotype that is targeted by the medicine being tested, rendering them inappropriate for the study. Eligible and appropriate patients may not be sufficiently motivated to participate, and even if they are, they may not be aware of a matched study or find the recruiting procedure too difficult to traverse. Moving enough patients through these bottlenecks in a timely manner is a huge difficulty, and it is the leading cause of trial delays: Enrolment schedules are missed in 86

percent of studies, and enrolment issues cause almost one-third of Phase III trials to fail. One-third of the trial's total time is spent recruiting patients. Because Phase III studies require the biggest patient cohorts, they account for 60% of the overall expenditures of getting a medication through all trial phases. A 32 percent failure rate in Phase III trials due to patient recruiting issues highlights one of the most serious flaws in current clinical trial design: Inefficient patient recruiting strategies cause problems on the studies with the highest patient demand. AI and machine learning-driven solutions can help enhance patient cohort makeup and patient recruitment.[11]

Identifying Drug Candidates and Patients:

The number of experimental medications in development has risen considerably in recent years on a global basis. Many of these might be game-changers in the treatment of a variety of critical diseases, including cancers of various sorts, as well as viral and autoimmune disorders. The fact that there are so many medications in clinical development, some of which are targeting the same or comparable indications, adds to the rivalry for patients to participate in clinical research and for companies to plan for commercialization. In many situations, these research initiatives use the tried-and-true method of identifying and targeting cells with increased proliferative activity that are linked to illness. Manufacturers have lately concentrated clinical research on addressing the root cause of disease — the underlying biological mechanisms linked to disease genesis and progression – in order to provide optimal and perhaps curative benefit. This transition has also necessitated the use of more complex processes in patient screening and clinical study execution. Many drug companies are currently exploring the use of automated algorithms and complex prediction models to help find prospective molecular targets faster in this setting.

These algorithms are also being used to forecast the likelihood of new treatments making it through regulatory approval and eventually becoming commercially successful. AI techniques are being used to select patients for clinical research, in addition to helping drug discovery, and have the potential to provide several substantial advantages in drug development. Companies are mining enormous databases of patient data utilizing choices such as sophisticated neural networks and Bayesian algorithm-powered software systems to discover enrollment candidates. Many companies are also implementing AI-based prediction models to increase the statistical significance of data obtained from more focused candidates while also lowering trial expenses. Previously, clinicians were in charge of sifting through data to find patterns in clinical trial patient groups and using that knowledge to forecast medication efficacy and safety results, but AI is well positioned to take on this function on a much bigger and more efficient scale. Manufacturers will likely have additional possibilities to employ AI to find and recruit appropriate participants for clinical trials as technology and AI businesses continue to grow their networks of healthcare organizations, pharmaceutical companies, and contract research organizations.[12]

Study design:

Clinical trials' cost, efficiency, and success potential are all negatively impacted by poor research design. We may utilize AI, ML, and natural language processing (NLP) techniques to analyze and pick appropriate primary and secondary endpoints in study design, ensuring the most relevant protocols for regulators, payers, and patients are developed, by leveraging huge healthcare data sets. This informs optimum country and site tactics, enrollment models, patient recruiting, and start-up plans, all of which contribute to improve the research design. Better research design leads to more predictable findings, shorter protocol development cycles, fewer protocol revisions, and overall study efficiency. It also leads to higher rates of recruitment, fewer non-enrolling locations, and fewer protocol changes. These enhancements boost the likelihood of success and allow for more realistic and precise planning.[13]

Pharmacovigilance (PV):

To assure quality and control, huge volumes of structured and unstructured data must be merged and examined in PV. Many of the issues that PV units have in utilizing the value of this data via new levels of insight and proactive analytics to improve quality and control are being addressed by AI and ML technologies. These technologies may be used to automate time-consuming manual processes, as well as to translate and digitize safety case processing and adverse drug reaction (ADR) documentation to make them more accessible. They can also execute data listening jobs to monitor talks on social media and other platforms, ensuring that any negative occurrences are noticed as soon as possible. The insights gained by applying AI for PV tasks allow domain experts to analyze subject, site, and study hazards and overall study performance more quickly, allowing project managers to save time while enhancing patient safety. For faster and more effective safety evaluations, optical character recognition (OCR), natural language processing (NLP), and deep neural networks are being utilized to evaluate and prepare structured and unstructured data.[13]

Clinical monitoring:

Analyzing site hazards and developing "action items" to address such risks takes a lot of human work. By manually analyzing the risk environment and offering predictive analytics to provide more effective clinical monitoring insights, AL and ML ideas might reduce these demands.[13]

Machine learning:

On the grounds, ML is realizing the promise of AI notion as part of a wide scientific trend termed Artificial Intelligence (AI). The major concern with ML is the realization of demand for flexible, adaptive learning algorithms or computing techniques *. As a result, new system and software functionalities emerge. Algorithms, as well as ML prospects, such as the capacity to learn and provide expert-level recommendations in a specific application area, are available. In many aspects, machine learning is now a well-established subject. Selection of relevant data and pre-processing, selection of appropriate algorithms, and solution quality evaluation are all part of the ML application technique. The quest for optimal use of the accumulated potential of massive and heterogeneous data, search for quick learning techniques, and analysis of application aspects,

depending on the area of application, are all part of the development of this enormous sector. Data interpretation is frequently linked to classification, which occurs when a specific object is assigned to one of several previously defined classes, clustering, which occurs when objects are divided into initially undefined groups (clusters), and forecasting, which occurs when a large volume of initial data describing the process background, for example, is used to predict its future state in space or time. ML approaches are employed widely in all circumstances when no rigorous formal procedures of classification or clustering are applied.[14]

Artificial Intelligence is a broad field that encompasses a wide range of disciplines, from logical thinking to text tonality analysis algorithms. Traditionally, the terms "strong artificial intelligence" and "weak artificial intelligence" have been used to distinguish between the two. The first is focused on the development of high-intelligence human-centric decision-making systems, with the goal of eventually creating intelligent machines. Weak artificial intelligence is focused on the creation of applications that realize one or more human or animal intellectual abilities. Machine learning is used to fulfill the promise of a poor artificial intelligence notion. Machine learning techniques, which are a subset of weak artificial intelligence approaches, are useful for data analysis and processing, particularly large data. Various types of supervised and unsupervised learning techniques are combined in this architecture. At this point, classification or any other sort of heterogeneous data processing has a number of distinct characteristics: heterogeneity of data types, regularly occurring big amounts of data, and data collation problems. Machine learning approaches are being developed in tandem with their practical use, resulting in a rising number of applications and the emergence of unique decision procedures for applied issues based on ensembles of algorithms. Now, declarative programming environments and languages are recommended. Some of them are designed to make big data applications easier to use. Future research should focus on developing preprocessing approaches that can be applied to a variety of data types automatically or semi-automatically.[15]

Role of Machine learning in Clinical Trials:

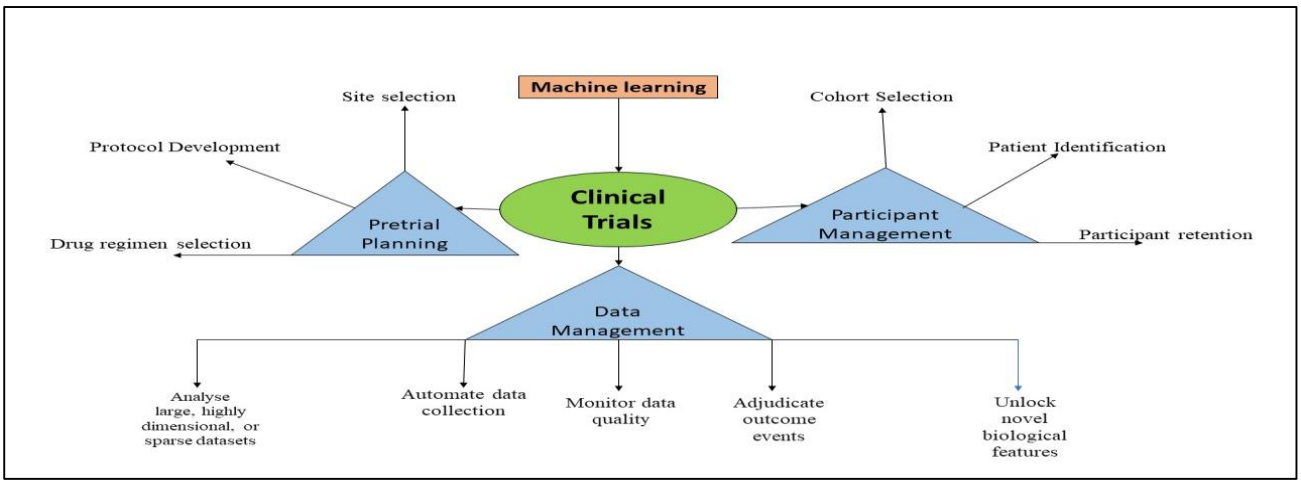

Figure No. 3 Role of machine learning in various domains of clinical trials

Clinical study protocol optimization:

As medicinal compounds reach human trials, ML can help maximise the effectiveness and efficiency of trials at the planning phase by applying simulation approaches to vast quantities of data from previous trials to help build trial protocols. For example, as proven in reinforcement learning approaches to Alzheimer's disease and non-small cell lung cancer, study simulation may optimise the choice of therapy regimens for testing.[16] Trials is a new start-up firm. AI enables investigators to upload protocols and utilises natural language processing to identify possible traps and roadblocks to trial completion (such as inclusion/exclusion criteria or outcome measurements). Unfortunately, the performance of these example models has not been peer-reviewed, and they therefore only offer a theoretical promise that using machine learning in research planning will assist guarantee that a specific trial design is best matched to the demands of the stakeholders. In conclusion, there are evident advantages to using machine learning to increase the efficiency and productivity of preclinical research and clinical trial preparation. The majority of peer-reviewed papers on ML's usage in this capacity, however, are focused on preclinical research and development rather than clinical trial preparation. This might be owing to the greater availability of big, highly dimensional datasets in translational contexts, as well as the higher potential costs, hazards, and regulatory difficulties involved with machine learning in clinical trials. To overcome these obstacles, peer-reviewed proof of ML application to clinical trial design is required.[17]

Selection of patient populations for investigation:

Improved patient population selection for trials may reduce the sample size necessary to detect a meaningful impact. Improved patient population selection, in other words, may reduce the number of patients who are exposed to therapies from which they are unlikely to benefit. Prior research has found that for every 1 planned response, there are 3 to 24 non-responders for the top drugs, resulting in a substantial percentage of patients receiving serious side effects in addition to the intended impact.[18] Unsupervised ML of patient populations can identify patterns in patient features that can be used to select patient phenotypes that are most likely to benefit from the proposed drug or intervention, in addition to facilitating patient population selection through rapid analysis of large databases of prior research (as discussed above).[19] Unstructured data is vital for phenotyping and defining representative cohorts, implying that taking into account extra patient data is a significant step toward finding robust, representative cohorts. [20]

Unsupervised learning of electronic health record (EHR) and genetic data from 11,210 individuals, for example, revealed three unique subgroups of diabetes mellitus type II, each of which may have a distinctive requirement for and response to a proposed medication.[21] Bullfrog AI is a start-up that aims to capitalize on the promise of targeted patient population selection by analyzing clinical trial data sets "to predict which patients will respond to a particular therapy in development, thereby improving inclusion/exclusion criteria and ensuring primary study outcomes are achieved," according to the company.[22] This unsubstantiated assertion conflates outcome prediction (which is unlikely to succeed and goes against the objective of clinical

research) with cohort selection (which is unlikely to succeed and goes against the intent of clinical research) (which would ideally identify patients on the basis of therapeutically relevant subtypes). Successfully identifying more selective patient populations has two potential drawbacks: first, trials may generate less important negative data about subgroups that would not benefit from the intervention; and second, trials may miss subgroups that would have benefited from the intervention but were missed by the ML model. These possible problems may be more likely to harm patient populations that live in rural, remote, or underdeveloped areas and have fewer healthcare encounters. These two pitfalls may have implications for drug/device development regulatory approval and commercialization, as pivotal trials in more highly selected and less representative patient subgroups may necessitate balancing the benefits of higher trial success with the disadvantages of fewer drug/device indications.

Collection, processing, and management of data from wearable and other smart devices:

Patient-generated health data through wearable and other mobile devices can enhance or even replace traditional data gathering. Wearable and other gadgets may make it possible to test and use novel, patient-centered biomarkers for diagnosis and treatment of some diseases (e.g., obesity, cardiovascular disease). A deep neural network, for example, was used to process data from a mobile single-lead electrocardiogram platform,[23] a random forest model was used to process audio output from Parkinson's disease patients,[24] and a recurrent neural network was used to process accelerometer data from atopic dermatitis patients.[25] ML processing of wearable sensor output to derive research endpoints introduces the risk of corrupt results if data is subverted by manipulations of the ML model, but this risk exists with any data regardless of processing technique.[26] Other device-related prospects in patient centricity, aside from the creation of novel digital biomarkers, include the capacity to export data and analytics back to participants to enhance education and insight. Better defining how previously established clinical objectives and patient-centric digital biomarkers overlap, as well as knowing participant attitudes on privacy in connection to the sharing and use of device data, are all barriers to ML processing of device data adoption. Novel biomarkers will also require FDA clearance. For ethical and privacy reasons, researchers interested in exploiting the power of these devices must explain the dangers and advantages to patients, as well as because deployment without addressing participant concerns has the potential to decrease participant recruitment and retention.[27]

Study data collection, verification, and surveillance:

Automating data gathering into case report forms, whether in prospective trials or retrospective reviews, is an intriguing use of ML, notably NLP, to research data management. This reduces the time, money, and possibility for mistake involved with human data extraction. ML can fuel risk-based monitoring approaches to clinical trial surveillance, enabling the prevention and/or early identification of site failure, fraud, and data discrepancies or incompleteness that may delay database lock and subsequent analysis, regardless of how data was gathered. Even when people collect data into case report forms (typically supplied in PDF format), the appropriateness of the obtained data for result determination may be checked using a combination of optical

character recognition and natural language processing (NLP).[28] Using auto-encoders to identify reasonable from implausible data, suspicious data patterns in clinical trials or inaccurate data in observational research can be found.[29]

Endpoint identification, adjudication, and detection of safety signals:

Data processing can also benefit from machine learning. When compared to the current approach of manual adjudication of events by a committee of clinicians, semi automated endpoint identification and adjudication has the potential to save time, money, and complexity. This is because, while endpoint adjudication has traditionally been a labor-intensive process, sorting and classifying events is well within the capabilities of machine learning. For example, utilizing a mix of optical character recognition and natural language processing, IQVIA Inc. has reported the capacity to automatically analyze some adverse events connected to medication regimens, albeit this approach has not been published in peer-reviewed journals.[13] Endpoint criteria and the data necessary to support them frequently vary from trial to trial, which theoretically necessitates retraining a classification model for each new trial, which might be a hurdle to semi-automated event adjudication deployment (which is not a viable approach). In the realm of cardiovascular research, attempts have lately been made to standardize results, however not all studies adhere to these criteria. Most areas have not yet undertaken comparable efforts to aggregate trial data to aid model training for cardiovascular outcomes.[30] Further progress in this field will need actual consensus on event definitions, the usage of consensus definitions, and stakeholders' willingness to contribute sufficient data for model training from many trials.

Data analysis:

Clinical trial data, registries, and clinical practices are rich sources for hypothesis development, risk modeling, and counterfactual simulation, and machine learning is ideally suited for these tasks. Unsupervised learning, for example, might discover phenotypic groupings in real-world data that can be investigated further in clinical trials.[31] Furthermore, machine learning (ML) has the potential to improve the widely used practice of secondary trial analyses by more effectively identifying treatment heterogeneity while still providing some (albeit insufficient) protection against false-positive findings, revealing more promising avenues for future research.[32] Moreover, machine learning may be utilized to develop risk predictions in retrospective datasets that can then be prospectively confirmed. Researchers were able to enhance classification between patients who would fare better or worse following cardiac resynchronization treatment using a random forest model in COMPANION trial data compared to a multivariable logistic regression model.[33] There are numerous useful machine learning algorithms for managing, processing, and analyzing clinical trial data, but there are less ways for increasing the quality of data as it is created and gathered Because data availability and quality are the bedrock of machine learning methodologies, conducting high-quality trials is critical to enabling higher-level ML processing.

Conclusion:

Although AI has the ability to influence many areas of clinical trial design, from planning to execution, any AI appeal that attempts to address all aspects at once is certain to fail.AI has wide spectrum application in the various domains of clinical trials such as patient selection, study design, Pharmacovigilance, clinical monitoring etc. AI is not a magic pill that will make clinical trial success rates jump overnight, just as a change in clinical trial design will not flip the efficiency of the Pharma R&D cycle from decay to growth. Both altering clinical trial design and employing AI to accomplish so are critical components of a much-needed revamp of the drug development cycle.

Since conventional double-blinded, randomized, controlled clinical trials with their set of relevant strategies persist its benchmark for biomedical evidence generation, advancement with machine learning techniques has the capacity to boost clinical trial's performance and effectiveness, expanding its massive influence for all stakeholders. To the degree that machine learning-enabled clinical research may increase the efficiency and quality of scientific evidence, it has the potential to save lives and alleviate suffering, creating an ethical obligation to investigate this prospect. Because there are few prospective studies on the relative effectiveness of ML vs traditional methodologies, and because change takes time, energy, and collaboration, the potential uses of ML to clinical research now outnumber its actual use. Although ML approaches have showed higher prediction performance in a variety of areas, they have yet to be used to conduct clinical trials. Many research used machine learning algorithms to predict treatment response and allocate therapies accordingly, resulting in unique clinical trial designs. Clinical trial designs based on machine learning outperform traditional clinical trial methods. And, to the greatest degree possible, the ensemble technique outperformed the clinical trial design. Our strategy is simple to apply in existing clinical trial systems, since the ML area matures and several packages are accessible on various programming platforms.

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