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RESEARCH ARTICLE

INTEGRATION OF ARTIFICIAL INTELLIGENCE IN ADAPTIVE TRIAL DESIGNS: ENHANCING EFFICIENCY AND PATIENT-CENTRIC OUTCOMES

Viswakanth Makutam[1], Sai Yashashwini Achanti[1] and Marjan Doostan[2]

1. Pharm. D, MS Applied Clinical Research, ACRP-CP, Quality Assurance Associate.
2. Pharm. D, MS Applied Clinical Research, Clinical Research Coordinator.

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Abstract

Background: Integrating artificial intelligence (AI) into adaptive trial designs represents a transformative approach in clinical research, promising enhanced efficiency and accuracy in trial outcomes. This study aims to systematically review the current landscape of AI applications in adaptive clinical trial designs.

Methods: A comprehensive search was conducted across multiple databases, resulting in 6177 records initially identified. After removing duplicates and ineligible records, 1476 studies were screened. Following rigorous screening and eligibility assessment, 45 studies were included in the final review. Inclusion criteria focused on peer-reviewed articles, systematic reviews, and clinical trials discussing the role of AI in adaptive trial designs. In contrast, exclusion criteria eliminated non-relevant and low-quality studies.

Results: The selected studies demonstrate that AI significantly improves adaptive trial designs through advanced data analytics, predictive modelling, and real-time decision-making. AI's integration facilitates dynamic randomization, optimised dosing strategies, and efficient patient recruitment, thereby enhancing the overall effectiveness of clinical trials.

Conclusion: AI integration in adaptive trial designs offers substantial benefits regarding trial efficiency, precision, and patient outcomes. Despite existing challenges such as data quality, ethical considerations, and regulatory requirements, the findings underscore the potential for AI to revolutionise clinical trials. Future research should address these challenges to harness AI's capabilities in adaptive trial designs fully.

Introduction:-

Clinical trials are the gold standard in clinical research, but when resources are few, conventional designs with set sample numbers and restricted arms sometimes cannot adequately address contemporary, complicated research issues. A solution is provided by adaptive clinical trial designs, which permit future adjustments in response to gathering data. In 2019, the US Food and Drug Administration (FDA) released guidelines for adaptable designs that included non-binding suggestions for their creation, use, and disclosure. Compared to traditional methods, adaptive designs have several advantages. These include increased statistical efficiency (e.g., managing type I error rates and power), ethical concerns addressed (e.g., increasing allocation to better-performing arms, stopping trials early for

Corresponding Author:- Viswakanth Makutam
Address:- Pharm. D, MS Applied Clinical Research, ACRP-CP, Quality Assurance Associate.

safety issues or limited benefit), and improved understanding of treatment effects (e.g., enriching trials with participants expected to benefit). [1], [2], [3], [4], [5]

Adaptive designs (ADs) provide clinical trials with flexibility by allowing for pre-planned alterations depending on interim results. This could improve trial quality and speed up or decrease the trial duration. Careful planning can solve practical obstacles, including money, communication, and execution. Learning from prior experiences and case studies is crucial, and more practitioners should write up their insights. Although inappropriate for all studies, especially those with lengthy outcome measures, ADs should be an essential methodological tool for clinical investigators. ADs protect against erroneous beginning assumptions but are not a solution for poorly thought-out trials. Although bias is possible, it may be reduced by careful preparation, openness, skilled Independent Data Monitoring Committees (IDMCs), and blinding triallists to modifications. Precise and thorough reporting of trial outcomes and design details is essential for future education, and reporting procedures are codified into an AD appendix to the CONSORT guidelines.[6]

Adaptive trial designs provide speed and flexibility through planned adjustments depending on interim data analysis, a significant advancement in clinical research. These designs enhance statistical power and ethical standards by allowing modifications like early halting for efficacy or futility, re-estimating sample numbers, and adjusting treatment allocations. The group sequential design, which incorporates scheduled intermediate evaluations to determine early termination based on predetermined criteria, is one essential component.[7], [8] As the trial continues, adaptive randomisation using minimisation modifies the likelihood of treatment assignments in favour of more successful therapies.[9]Reestimating the sample size enables adjustments to guarantee sufficient power, lowering the possibility of underpowered research.[10]

Moreover, adaptive trials allow for adding or removing treatment arms in response to interim data, improving resource allocation flexibility.[11] By concentrating on particular subgroups that are probably to benefit more from the therapy, enrichment strategies increase the accuracy of trial results.[12] Phase II/III designs that are seamless integrate these stages into a single, ongoing trial, using phase II results to guide phase III decisions without stopping the investigation.[13],[14] Adaptive dose-finding maximises dose determination more effectively by modifying dosage in response to participant reactions.[15]

Artificial intelligence (AI) is a field dedicated to replicating human-like abilities in perception, reasoning, learning, and problem-solving, particularly within clinical contexts.[16]AI is increasingly seen as a critical driver for sustainable and optimised drug development, with practical applications in clinical trials (CTs) now emerging. The growth of randomised trials has led to vast amounts of complex clinical, molecular, and imaging data. This data abundance is crucial for data-driven and personalised medicine trends. However, comprehensive AI models trained on suitable datasets are essential to derive actionable insights. These models can significantly expedite and streamline various activities within drug research, enhancing the efficiency and effectiveness of the process.[17]

Integrating AI into adaptive trial designs represents a revolutionary advancement in clinical research, offering unprecedented efficiency and precision. Traditional clinical trials, often limited by fixed sample sizes and rigid protocols, need help addressing contemporary research questions' dynamic and complex nature. However, Adaptive trial designs allow for real-time modifications based on interim data, enhancing statistical power and ethical standards. AI's role in this paradigm is transformative, facilitating advanced data analytics, predictive modelling, and real-time decision-making, significantly improving trial quality and speed. AI enables dynamic randomisation, optimised dosing strategies, and efficient patient recruitment, making clinical trials more responsive to emerging data and patient needs. This study systematically reviews the current landscape of AI applications in adaptive trial designs, highlighting the substantial benefits and addressing the challenges, such as data quality, ethical considerations, and regulatory requirements. By providing a comprehensive overview of AI-driven innovations in clinical trials, this research underscores the potential for AI to revolutionise the field, ultimately leading to faster, more accurate, and patient-centric outcomes. As the healthcare industry embraces AI, understanding its integration into adaptive trial designs becomes crucial for advancing medical research and improving patient care.

This review article explores the evolving role of adaptive clinical trial designs (ADs) and artificial intelligence (AI) in modern clinical research. It will assess the advantages, challenges, and practical applications of ADs and AI, emphasising how they can enhance clinical trials' efficiency, flexibility, and ethical standards.

Methodology:-

This review used preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations. The three authors, ViswakanthMakutam, Sai Yashahwini Achanti, and Marjan Doostan independently assessed all eligible studies. If there were any cases of disagreement, a consensus was reached. We searched through the electronic database PubMed (until June 2024) using the search terms "Artificial Intelligence in Clinical Trials," "Machine Learning in Clinical Trials," and "Adaptive Clinical Trial designs."

From the PubMed database, a comprehensive search yielded a total of 6177 articles, which included 2447 articles for "Machine Learning in Clinical Trials"; 3593 articles were earmarked for "Artificial Intelligence in Clinical Trials" and 137 articles for "Adaptive Clinical Trial designs". However, after meticulous scrutiny, 6132 articles were deemed irrelevant to the review's focus based on the inclusion and exclusion criteria and consequently excluded. Ultimately, 45 articles remained for detailed analysis, each considered pertinent to the study's objectives.

The flowchart depicts the systematic process of identifying, screening, and selecting studies for a review on the role of artificial intelligence (AI) in clinical trials and adaptive trial designs. Initially, 6177 records were identified from databases, but no records were found in registers. Before screening, 3251 records were marked ineligible by automation tools, and 1450 were removed for other reasons, leaving 1476 records to be screened. Following the screening, no records were excluded at this stage. All 1476 records were assessed for eligibility, excluding 1035 records that were not related to AI in clinical trials or adaptive trial designs and 396 records with unclear methodology or insufficient data. Ultimately, 45 studies were included in the review. This flowchart ensures a rigorous selection, enhancing the review's credibility and relevance.

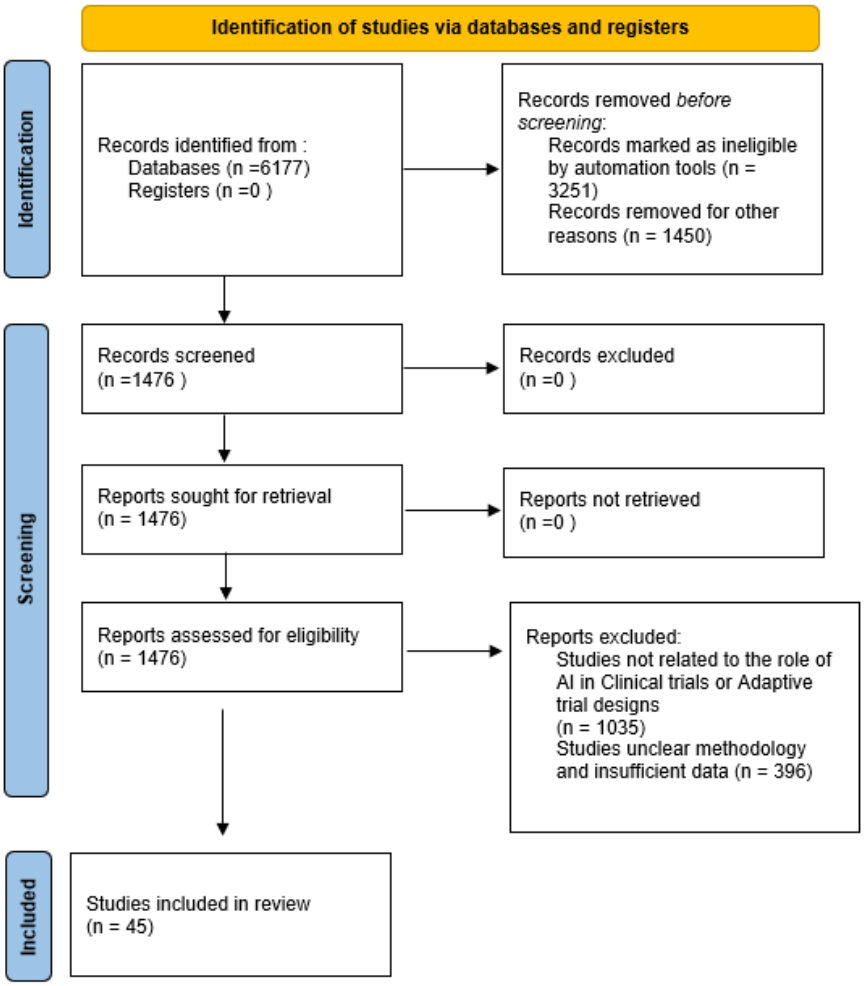

Figure 1:- Flow Diagram of Papers Researched.

Results:-

Clinical Trial Design with AI:

Designing clinical trials is complex, requiring accuracy, reliability, power, and generalizability. Adaptive designs, which modify trials using interim data, show promise but need robust, unbiased statistical analysis. AI can significantly enhance this process by simulating multiple rounds of data analysis, such as tenfold validation or the parametric G formula.[18]In statistical planning, AI's predictive analytics can improve interim and final analyses, operationalise study design through stratified cohort identification, and optimize designs involving multiple biomarkers and treatments from various modalities. The primary limitation of current trials is their generalizability and external validity. Advanced methodologies like Markov chain Monte Carlo, decision rules, Bayesian analysis, and novel AI techniques can address these issues. AI can select targeted populations by analyzing multiple variables, such as ethnicity, lifestyle, diet, income, and geographical location, improving the external validity of findings.

Additionally, AI can identify drug efficacy and adverse reactions, reducing time and costs compared to traditional trials. For instance, AI applied to wearable technology can integrate real-world variables into trial protocols. AI also facilitates genome-driven basket/umbrella trials, enhancing statistical methods and power by selecting genes or single nucleotide variants in small populations with rare heterogeneous syndromes.[19]

Prediction of Clinical Trial Outcomes:

AI and machine learning (ML) significantly enhance clinical trials (CTs) by supporting early disease detection, predicting molecular features, target sensitivity, bioavailability, and toxicity. These technologies reduce late-stage trial failures, increasing the likelihood of Phase II/III trials advancing to regulatory approval. The benefits extend to conserving human and financial resources and ensuring participant safety, positively impacting public perception of CTs. ML models, informed by CT design and patient data, can predict regulatory approval and estimate success probabilities in phase transitions, considering factors such as protocol complexity, clinical endpoints, interventional arms, and eligibility criteria. Additionally, risk score-based models can help design safer and more effective trials. In oncology, AI builds in-silico trials using clinical data to simulate cohorts and model treatment effectiveness, identifying better responders and reducing development failures. However, lacking high-quality, curated datasets remains a significant challenge, limiting AI's full potential. Overall, AI and ML offer transformative improvements in trial design, execution, and success rates.[20], [21], [22]

Forecasting Clinical Outcomes in Precision Medicine:

AI is pivotal in predicting clinical outcomes, crucial for precision medicine, and optimizes trial design by minimizing statistical variability. AI can simulate data to identify efficient statistical outcome measures and predict participant outcomes, potentially shortening trial durations. By analyzing electronic medical records (EMRs), AI can also predict clinical trial dropouts, allowing targeted interventions to retain participants and reduce the overall sample sizes needed. In cardiovascular trials, targeting potential dropouts with additional education has shown promise in extending participation. Machine learning (ML) prediction models have demonstrated a significant impact, reducing cancer mortality by 15-25% across various trials. These models utilize large biological databases to correlate drug-related predictive biomarkers with survival data stratified by genetic and environmental factors. For instance, ML tumor growth models have been validated in non-small cell lung cancer trials to predict tumor response and survival rates based on biomarker status and other complex drivers. AI tools enhance drug selection and adapt investigational drugs to specific cancer histologies, potentially increasing survival rates. As ML models incorporate comprehensive multi-omic data, they are poised to transform treatment paradigms and redefine precision trial design and recruitment, making them more efficient and targeted.[22], [23], [24]

Randomization:

Randomization is crucial in RCTs to ensure that treatment arms have similar patient characteristics, making the treatment assignment the only differing factor. Traditional coin flip randomization is simple but lacks control over allocations and covariate adjustment. Stratified block randomization improves on this by using pre-specified sequences within patient subgroups, though it struggles with categorizing continuous variables, managing many covariates, and potential selection bias. Covariate-adaptive designs, such as the minimization method, address these limitations by balancing multiple covariates simultaneously. This method reduces imbalance across covariates but is more complex and requires additional resources. Response-adaptive designs modify allocation ratios based on ongoing trial success, aiming to allocate more participants to effective arms. While potentially increasing no responders and introducing biases from temporal trends, this method can be advantageous in multiarmed trials

where the control group maintains a fixed allocation. However, caution is needed due to risks of unblinding and estimation variability. [9], [25], [26], [27], [28], [29], [30], [31], [32], [33]

Randomization in clinical trials often involves assigning participants to a control group, which can be resource-intensive. AI models, trained on extensive clinical, genetic, and imaging data, offer the potential to replace traditional control arms with virtual controls, significantly reducing recruitment needs. For instance, deep learning models have shown promise in predicting long-term disease progression from baseline data. Validating these AI models in independent populations is essential to ensure accuracy. While consuming clinical metadata, DL models have demonstrated a proof of concept by being able to forecast the appearance of a Humphrey visual field (HVF) from a single baseline HVF up to 5.5 years in advance.[34] Incorporating synthetic control arms alongside traditional placebo groups in trials can help evaluate AI predictions without affecting results. Large-scale collaborations and standardisedprotocols are crucial for developing robust AI algorithms. Despite challenges like dependency on well-labelled data and AI's "black-box" nature, methods to elucidate AI decision-making can integrate AI effectively into RCTs, enhancing efficiency and participation rates.[35]

Treatment arm:

Adaptive treatment arm selection improves efficiency and relevance by adjusting research designs by including or excluding treatment arms. Adaptable dose-finding, seamless drop-the-losers, and adaptable platform designs are essential techniques. Like the ongoing reassessment approach, adaptive dose-finding establishes the ideal dose early in research. Adaptive seamless designs eliminate phase transition time and reduce total sample size by combining the objectives of two trial phases. Drop-the-losers strategies concentrate on the most promising therapies, discarding less effective treatments following interim assessments. Adaptive platform trials focus on the condition rather than individual therapies by examining several interventions for a given condition and allowing treatments to be added or eliminated based on real-time data. These techniques enhance the relevance, efficiency, and adaptability of trials.[36], [37], [38]

AI can create external control arms, making trials more patient-centric and efficient. Unlearn'sTwinRCTsTM combines AI, digital twins, and advanced statistical methods to improve trial success rates with fewer patients.[39]Digital twins predict disease progression using historical control data, enhancing confidence in treatment effects. This approach, suggested by the European Medicines Agency for phase II and III trials, is appealing because it reduces reliance on traditional control groups, increasing patient likelihood of receiving treatment and speeding up enrollment. However, rigorous guidelines are needed to standardize synthetic patient generation and ensure comparability with traditional placebo arms.[40]

Patient Selection:

Patient selection in clinical trials faces multiple challenges, such as eligibility, suitability, and patient motivation. Traditional methods often lead to delays and high failure rates, especially in Phase III trials where recruitment problems are common. AI and machine learning (ML) systems can significantly enhance patient cohort composition and recruitment efficiency by analyzing comprehensive clinical, genetic, and imaging data. This allows AI to accurately identify eligible and suitable patients, predict disease progression, and facilitate better trial matches without manual reviews. AI can assist in clinical trial enrichment by selecting patients who are more likely to demonstrate the drug's effect. Sophisticated analytics methods combine omic data with electronic medical records (EMR) and other patient data to identify suitable biomarkers and patient subpopulations. Techniques like natural language processing (NLP) and optical character recognition (OCR) automate data extraction and harmonization, enhancing patient profiling and selection. Electronic phenotyping within health informatics reduces population heterogeneity by identifying patients with specific characteristics, further refined by advanced ML methods for improved prognostic and predictive enrichment.[41], [42]

Currently, AI is most frequently applied to patient recruitment in clinical trials. Tools like Deep Six use NLP to analyses physicians' notes, pathology reports, and lifestyle data to match patients to suitable trials, while Mendel.ai interprets unstructured data from clinicaltrials.gov to find qualified patients. AI can also leverage EHRs to identify eligible patients or define criteria based on past trials. Despite some AI systems facing criticism for biases and lack of standard evaluation techniques, advancements in explainable AI and regulatory frameworks pave the way for more effective patient selection. By improving recruitment, stratification, and optimization processes, AI enhances both the efficiency and accuracy of clinical trials, ultimately leading to better trial outcomes and more reliable design.[19], [43], [44]

Discussion:-

Adaptive clinical trial designs (ADs) and artificial intelligence (AI) are revolutionizing clinical research by enhancing efficiency, flexibility, and ethical standards. ADs offer advantages over traditional trials by allowing pre-planned modifications based on interim results. This flexibility improves trial quality and can shorten duration. Examples include adaptive dose-finding designs that optimize dose determination early and adaptive seamless designs that merge trial phases to reduce overall sample sizes and transition times. Drop-the-losers and adaptive platform trials focus resources on the most promising treatments, increasing relevance and efficiency. Ethical considerations are addressed by increasing allocation to better-performing arms and enabling early trial termination for safety issues or limited benefits. These designs ensure participants receive the most effective treatments, improving patient outcomes and trust in clinical research. Additionally, by allowing modifications like re-estimating sample sizes and adjusting treatment allocations, ADs enhance statistical power and the precision of treatment effect estimates. Enrichment strategies focusing on subgroups likely benefit from the therapy further refine trial results.

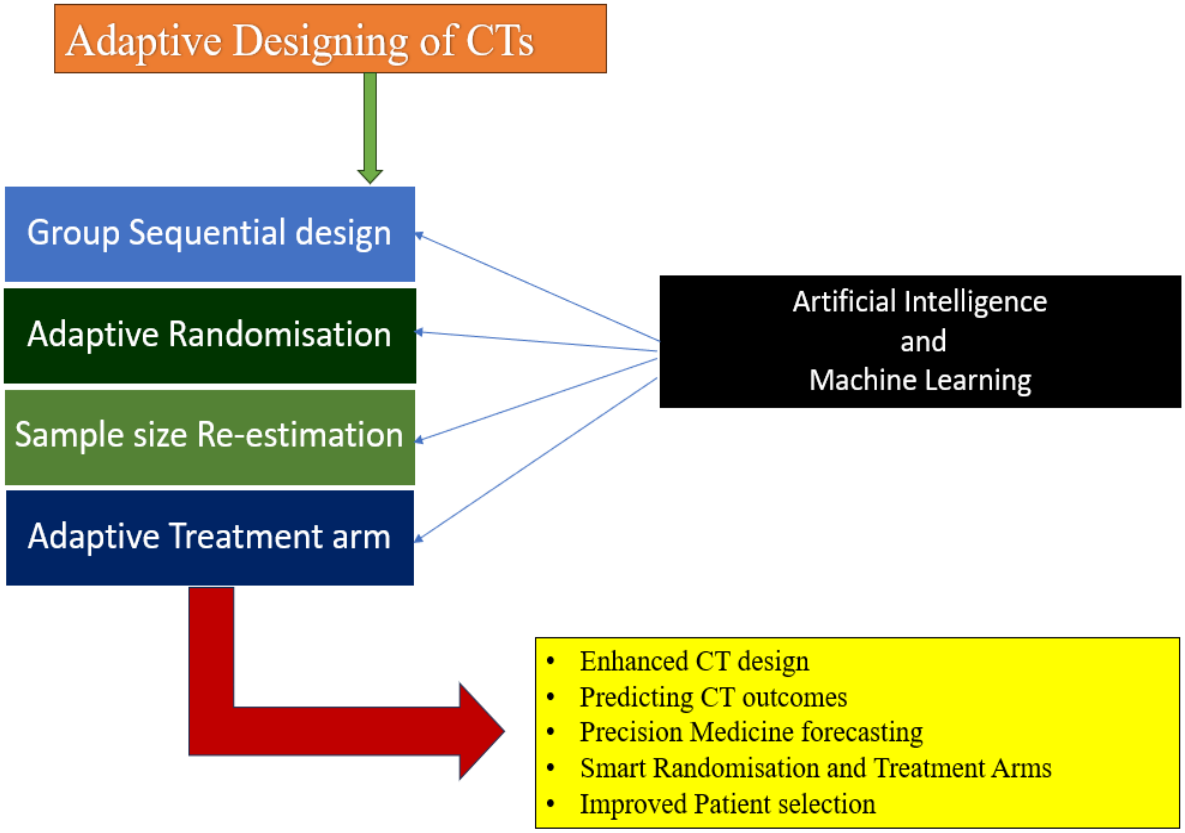

Figure 2:- AI and ML enhancing adaptive Clinical trial designs.

This diagram illustrates the integration of Artificial Intelligence (AI) and Machine Learning (ML) in the adaptive design of clinical trials (CTs). The adaptive design methods include Group Sequential Design, Adaptive Randomization, Sample Size Re-estimation, and Adaptive Treatment Arms. AI and ML enhance these methods by enabling more efficient CT designs, predicting outcomes, forecasting precision medicine, optimizingrandomization and treatment arms, and improving patient selection. The flow chart visually represents how AI and ML support each adaptive method and ultimately lead to enhanced clinical trial processes and outcomes, with the benefits summarized in the yellow box.

Table 2:- Description of various clinical trial adaptive designs and AI usage.

Adaptive designs	Description
Enhancing Clinical Trial Design with AI	AI enhances clinical trial design by simulating multiple rounds of data analysis and improving statistical planning. It helps operationalize study design through stratified cohort identification and optimizes designs involving multiple biomarkers and treatments. AI can address generalizability and external validity issues using methodologies like Markov chain Monte Carlo, decision rules, Bayesian analysis,

	and novel AI techniques. It also identifies drug efficacy and adverse reactions, integrating real-world variables through wearable technology and genome-driven trials.
Prediction of Clinical Trial Outcomes	AI and ML support early disease detection, predict molecular features, target sensitivity, bioavailability, and toxicity, reducing late-stage trial failures. ML models predict regulatory approval and success probabilities, aiding safer and more effective trials. AI builds in-silico trials to simulate cohorts, identifying better responders and reducing development failures. However, high-quality, curated datasets are needed to realize AI's potential fully. AI and ML offer transformative improvements in trial design, execution, and success rates.
Predicting Clinical Outcomes in Precision Medicine	AI predicts clinical outcomes, which is crucial for precision medicine. It optimizes trial design by minimizing statistical variability. AI simulates data to identify efficient statistical outcome measures and predict participant outcomes. It analyses EMRs to predict clinical trial dropouts, allowing targeted interventions to retain participants. ML models have significantly impacted cancer trials, reduced mortality and enhancing drug selection. ML models incorporate multi-omic data, transforming treatment paradigms and redefining precision trial design and recruitment.
Randomization	Randomization in RCTs ensures treatment arms have similar patient characteristics. Traditional coin flip randomization lacks control over allocations and covariate adjustment. Stratified block randomization and covariate-adaptive designs address these limitations, balancing multiple covariates simultaneously. Response-adaptive designs modify allocation ratios based on ongoing trial success. AI models offer the potential to replace traditional control arms with virtual controls, significantly reducing recruitment needs. Validating AI models in independent populations ensures accuracy.
Treatment Arm	Adaptive treatment arm selection improves efficiency by adjusting research designs. Techniques include adaptive dose-finding, seamless, drop-the-losers, and adaptive platform designs. AI can create external control arms, making trials more patient-centric and efficient. Digital twins predict disease progression using historical control data, enhancing confidence in treatment effects. This approach reduces reliance on traditional control groups, increasing patient likelihood of receiving treatment and speeding up enrollment. Rigorous guidelines are needed to standardize synthetic patient generation.
Patient Selection	AI and ML systems enhance patient cohort composition and recruitment efficiency by analyzing comprehensive datasets, identifying eligible and suitable patients, predicting disease progression, and facilitating better trial matches without manual reviews. Techniques like NLP and OCR automate data extraction, enhancing patient profiling and selection. AI tools like Deep Six and Mendel.ai use NLP to match patients to suitable trials. Despite challenges like biases and lack of standard evaluation techniques, advancements in explainable AI and regulatory frameworks are improving patient selection.

AI significantly enhances the trial design process by simulating multiple rounds of data analysis and improving statistical planning. AI operationalises study designs through stratified cohort identification and optimises designs involving multiple biomarkers and treatments, addressing the primary limitation of traditional trials: their generalizability and external validity. AI and machine learning (ML) models improve early disease detection and predict molecular features, bioavailability, and toxicity. These technologies reduce late-stage trial failures, increasing the likelihood of Phase II/III trials advancing to regulatory approval. AI also predicts clinical trial dropouts, enabling targeted interventions to retain participants and reduce sample sizes.

Furthermore, AI improves patient selection and recruitment by analysing clinical, genetic, and imaging data. Tools like Deep Six and Mendel.ai use natural language processing (NLP) to match patients to suitable trials, enhancing recruitment efficiency and outcomes. Electronic health records (EHRs) identify eligible patients and define criteria based on past trials, facilitating better trial matches without manual reviews. While AI offers numerous benefits,

challenges such as dependency on well-labelled data, biases, and the "black-box" nature of AI models must be addressed to maximise their potential.

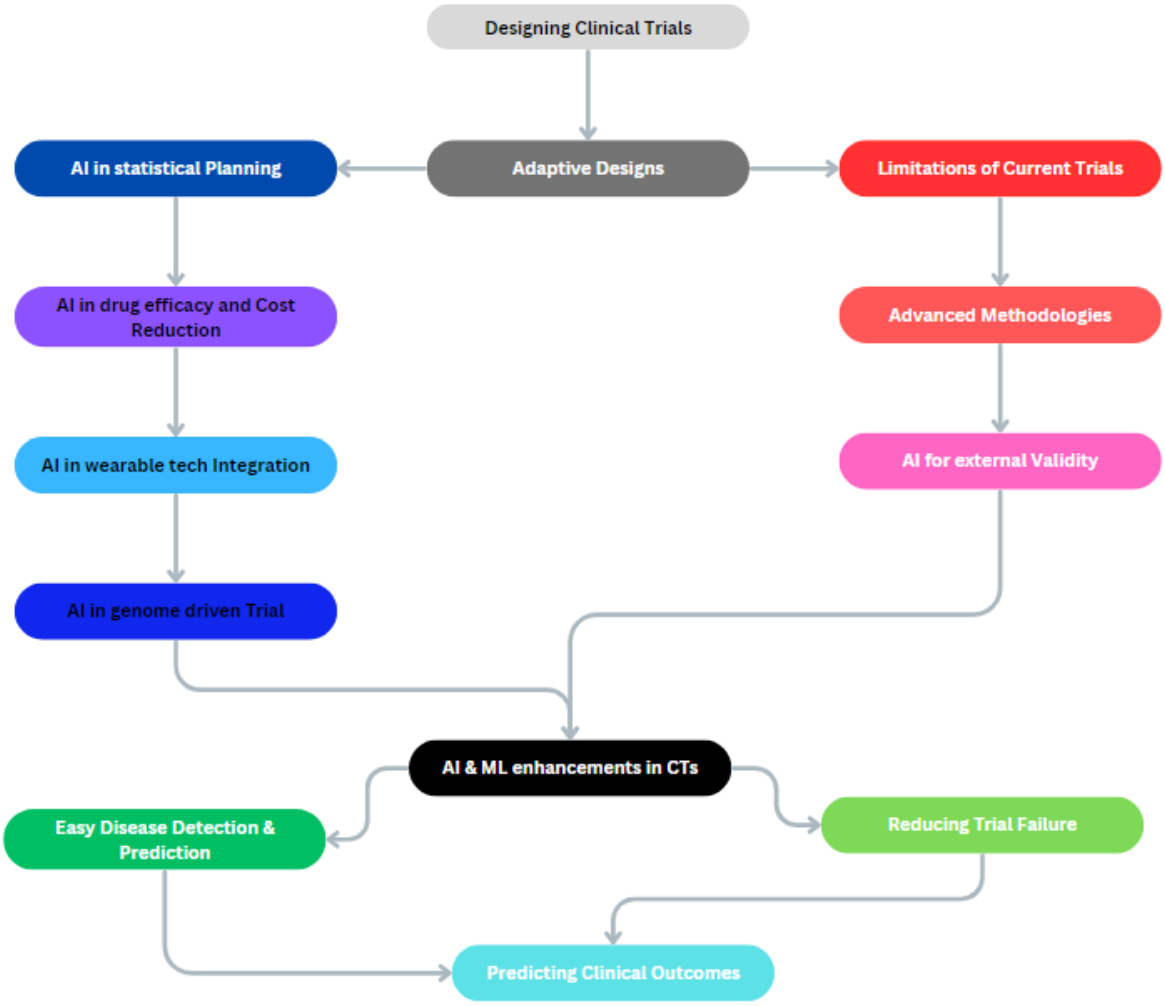

Figure 3:- AI and ML application in adaptive CTs.

Figure 3 outlines the role of AI and ML in enhancing clinical trials (CTs) through adaptive designs. Starting from designing clinical trials, the flowchart branches into adaptive designs and highlights limitations of current trials and advanced methodologies, including AI for external validity. Critical areas of AI application include statistical planning, drug efficacy, cost reduction, wearable tech integration, and genome-driven trials. These enhancements contribute to early disease detection, predicting clinical outcomes, and reducing trial failures. The diagram emphasises the comprehensive impact of AI and ML on improving the effectiveness and efficiency of clinical trials.

Unsuccessful randomized controlled trials (RCTs) often need help with poor patient selection, inadequate randomization leading to confounding factors, insufficient sample sizes, and poor endpoint selection.[45]By leveraging well-curated large datasets that include clinical and multimodal imaging data, AI models can be trained to efficiently identify suitable study participants, predict their natural history using advanced statistical methods, and assess study endpoints in a data-driven manner. These capabilities of AI offer the potential for more efficient execution and greater statistical power compared to traditional RCTs, reducing the reliance on costly manual reviews.[35]

Orphan drug approval and design pose unique challenges that can benefit significantly from adaptive clinical trial designs (ADs) and artificial intelligence (AI). Orphan drugs that treat rare diseases often need help with limited

patient populations, complicating traditional trial methodologies. ADs and AI can provide tailored solutions to these challenges, enhancing orphan drug trials' efficiency and success rates. The rejection of Sohonos by the European Medicines Agency (EMA) is a pertinent example of the challenges faced in orphan drug approval.[46] Sohonos is intended to treat fibrodysplasia ossificans progressive (FOP).[47] FOP is a rare and highly debilitating autosomal dominant condition marked by frequent episodes of soft tissue pain, edema, and the growth of tumors in muscle and connective tissue.[48] This drug faced significant hurdles due to limited clinical trial data and concerns about the robustness of the evidence presented. The EMA's decision underscores the critical need for innovative trial designs and analytical methods to overcome the inherent difficulties in developing treatments for rare diseases for which incorporation of AI and adaptive trial designs may foster the drug approval process.

Conclusion:-

This review systematically examined the integration of artificial intelligence (AI) in adaptive trial designs within clinical research. By rigorously identifying and analysing 45 relevant studies, it has been demonstrated that AI significantly enhances the efficiency and effectiveness of clinical trials through advanced data analysis, adaptive randomisation, and real-time decision-making. The findings highlight the potential of AI to streamline trial processes, improve patient outcomes, and accelerate the development of new treatments. However, challenges such as data quality, ethical considerations, and the need for regulatory frameworks remain. Future research should address these challenges and explore the broader implementation of AI-driven adaptive trial designs across diverse clinical settings. Overall, integrating AI in adaptive trial designs promises revolutionising clinical research, making it more responsive, precise, and patient-centric.

References:-

1. Center for Drug Evaluation and Research. Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry. Available from: FDA. Accessed: Jun. 30, 2024.
2. Li Q, Lin J, Lin Y. Adaptive design implementation in confirmatory trials: methods, practical considerations and case studies. Contemp Clin Trials 2020;98:106096.
3. Center for Drug Evaluation and Research. Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products. Available from: FDA. Accessed: Jun. 30, 2024.
4. Center for Biologics Evaluation and Research. Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products. Available from: FDA. Accessed: Jun. 30, 2024.
5. Chow SC, Chang M, Pong A. Statistical consideration of adaptive methods in clinical development. J Biopharm Stat 2005;15(4):575-91.
6. Pallmann P, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC Med 2018;16(1):29.
7. Pre-hospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac arrest (PARAMEDIC-2): Trial protocol. Available from: PMC. Accessed: Jul. 01, 2024.
8. Burnett T, Jennison C. Adaptive enrichment trials: What are the benefits? Stat Med 2021;40(3):690-711.
9. Taves DR. The use of minimisation in clinical trials. Contemp Clin Trials 2010;31(2):180-4.
10. Power Priors and Their Use in Clinical Trials. Available from: The American Statistician. Accessed: Jul. 01, 2024.
11. Adaptive platform trials: definition, design, conduct and reporting considerations. Available from: PubMed. Accessed: Jul. 01, 2024.
12. Adaptive Enrichment Designs in Clinical Trials. Available from: PMC. Accessed: Jul. 01, 2024.
13. Cuffe RL, Lawrence D, Stone A, Vandemeulebroecke M. When is a seamless study desirable? Case studies from different pharmaceutical sponsors. Pharm Stat 2014;13(4):229-37.
14. Richter J, Friede T, Rahnenführer J. Improving adaptive seamless designs through Bayesian optimisation. Biom J 2022;64(5):948-63.
15. Adaptive Dose-Finding Studies: A Review of Model-Guided Phase I Clinical Trials. Available from: PMC. Accessed: Jul. 01, 2024.
16. Reddy S, Fox J, Purohit MP. Artificial intelligence-enabled healthcare delivery. J R Soc Med 2019;112(1):22-8.
17. Delso G, Cirillo D, Kaggie JD, Valencia A, Metser U, Veit-Haibach P. How to Design AI-Driven Clinical Trials in Nuclear Medicine. Semin Nucl Med 2021;51(2):112-9.
18. Johnson KW, Glicksberg BS, Hodos RA, Shameer K, Dudley JT. Causal inference on electronic health records to assess blood pressure treatment targets: an application of the parametric g formula. Pac Symp Biocomput2018;23:180-91.

19. Krittanawong C, Johnson KW, Tang WW. How artificial intelligence could redefine clinical trials in cardiovascular medicine: lessons learned from oncology. Pers Med 2019;16(2):83-8.
20. Zhavoronkov A, Vanhaelen Q, Oprea TI. Will Artificial Intelligence for Drug Discovery Impact Clinical Pharmacology? Clin Pharmacol Ther 2020;107(4):780-5.
21. The Case for AI-Driven Cancer Clinical Trials – The Efficacy Arm In Silico. Available from: PMC. Accessed: Jul. 01, 2024.
22. Siah KW, Khozin S, Wong CH, Lo AW. Machine-Learning and Stochastic Tumor Growth Models for Predicting Outcomes in Patients With Advanced Non-Small-Cell Lung Cancer. JCO Clin Cancer Inform 2019;3:1-11.
23. A Comparative Study on Machine Learning Algorithms for Predicting Breast Cancer Prognosis in Improving Clinical Trials. Available from: IEEE Xplore. Accessed: Jul. 01, 2024.
24. Schperberg AV, Bouchard A, Tsigelny IF, Richard SB, Kurzrock R. Machine learning model to predict oncologic outcomes for drugs in randomised clinical trials. Int J Cancer 2020;147(9):2537-49.
25. An Extended Minimization Method to Assure Similar Means of Continuous Prognostic Variables between Treatment Groups. Available from: JSTAGE. Accessed: Jul. 01, 2024.
26. Endo A, Nagatani F, Hamada C, Yoshimura I. Minimization method for balancing continuous prognostic variables between treatment and control groups using Kullback-Leibler divergence. Contemp Clin Trials 2006;27(5):420-31.
27. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31(1):103-15.
28. Taves DR. Minimization: a new method of assigning patients to treatment and control groups. Clin Pharmacol Ther 1974;15(5):443-53.
29. Ciolino JD, Palac HL, Yang A, Vaca M, Belli HM. Ideal vs. real: a systematic review on handling covariates in randomised controlled trials. BMC Med Res Methodol2019;19:136.
30. The Clinical Trial. Available from: NEJM. Accessed: Jul. 01, 2024.
31. Design of Experiments with R. Available from: SpringerLink. Accessed: Jul. 01, 2024.
32. Korn EL, Freidlin B. Time trends with response-adaptive randomisation: The inevitability of inefficiency. Clin Trials Lond Engl 2022;19(2):158-61.
33. Rosenberger WF, Sverdlov O, Hu F. Adaptive randomisation for clinical trials. J Biopharm Stat 2012;22(4):719-36.
34. Forecasting future Humphrey Visual Fields using deep learning. Available from: PMC. Accessed: Jul. 01, 2024.
35. Lee CS, Lee AY. How Artificial Intelligence Can Transform Randomized Controlled Trials. Transl Vis Sci Technol 2020;9(2):9.
36. Neal D, Casella G, Yang MCK, Wu SS. Interval estimation in two-stage, drop-the-losers clinical trials with flexible treatment selection. Stat Med 2011;30(23):2804-14.
37. Lin J, Bunn V. Comparison of multi-arm multi-stage design and adaptive randomisation in platform clinical trials. Contemp Clin Trials 2017;54:48-59.
38. Adaptive Seamless Phase II/III Designs—Background, Operational Aspects, and Examples. Available from: SAGE Journals. Accessed: Jul. 01, 2024.
39. Unlearn Closes $50 Million Series B Funding to Advance the Use of Its Machine Learning-Powered TwinRCTs™ in Clinical Trials. Available from: Business Wire.
40. Zhang B, Zhang L, Chen Q, Jin Z, Liu S, Zhang S. Harnessing artificial intelligence to improve clinical trial design. Commun Med 2023;3(1):1-3.
41. Miotto R, Weng C. Case-based reasoning using electronic health records efficiently identifies eligible patients for clinical trials. J Am Med Inform Assoc 2015;22(e1):e141-50.
42. Harrer S, Shah P, Antony B, Hu J. Artificial Intelligence for Clinical Trial Design. Trends Pharmacol Sci 2019;40(8):577-91.
43. Glicksberg BS, et al. Automated disease cohort selection using word embeddings from Electronic Health Records. Pac Symp Biocomput2018;23:145-56.
44. Mendel.ai nabs $2 million to match cancer patients with the latest clinical trials | TechCrunch. Available from: https://techcrunch.com/2017/07/01/mendel-ai-nabs-2-million-to-match-cancer-patients-with-the-latest-clinical-trials/. Accessed: Jul. 01, 2024.
45. Challenging issues in randomised controlled trials - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/20413119/. Accessed: Jul. 01, 2024.
46. Sohonos | European Medicines Agency. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/sohonos. Accessed: Jul. 01, 2024.

47. Pignolo RJ, et al. Reduction of New Heterotopic Ossification (HO) in the Open-Label, Phase 3 MOVE Trial of Palovarotene for Fibrodysplasia Ossificans Progressiva (FOP). J Bone Miner Res 2023;38(3):381-94.
48. Viswakanth M. REVIEW ARTICLE ON FIBRODYSPLASIA OSSIFICANS PROGRESSIVA. World J Pharm Pharm Sci 2018;7(6):123-34.