Revolutionizing Medicine: Unleashing the Power of Real-World Data and AI in Advancing Clinical Trials

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In the biopharmaceutical industry, the conventional "linear and sequential" clinical trial approach is still the norm; however, it is frequently beset by issues with patient selection, retention, and monitoring that are not up to par, leading to longer trial durations and higher trial failure rates. Artificial intelligence (AI) has the potential to reduce the duration of clinical trials significantly, expedite protocol design and study implementation, improve trial outcomes, and lower the cost of biopharmaceutical R&D. AI may also speed up clinical cycle times. Clinical trial mining, design and execution, and real-world experience analysis are all possible using AI. Major drug makers are utilizing AI to locate volunteers for clinical trials or to cut down on the number of subjects required for drug testing, which might speed up medication development and save millions of dollars. The clinical trial procedure may be enhanced by AI, but evidentiary requirements for a drug's efficacy and safety won't alter, according to regulators. This article discusses the application of AI, RWD, and RWE in clinical trials and how it is transforming the biopharma value chain, encompassing all pharmaceutical firms referred to as "biopharma companies" due to the inclusion of biologics in their development pipelines and within these biopharma firms, artificial intelligence (AI) is finding its way into drug research.

Keywords: Clinical trial. Real-world data. Artificial intelligence. Biopharmaceutical industries. Developments. Healthcare.

INTRODUCTION

Governments and private payers are closely examining the economic benefit of novel therapies as healthcare costs continue to climb as a proportion of each nation's gross domestic product (GDP). Regulators are increasingly expecting clinical studies to show not only efficacy and safety but also a significant influence on patient's lives. This is especially true for expensive, targeted medicines for limited patient populations. The complexity of clinical trial design and development is rising as a result of the increasing demands of payers and regulators on biopharma companies to raise the quality and amount of evidence produced during clinical trials. Payers are considering procedures with sponsors to assure value for money, including screening patients to identify those who may react better and tying payments to specific results. The traditional techniques of conducting clinical trials must be modified to demonstrate value, especially when it comes to gathering real-world clinical and non-clinical data on costs and results. As a result, the rush to gather significant data is intensifying to improve biopharma's understanding of the epidemiology of illness and to please regulators and Health Technology Assessment (HTA) authorities. Clinical trials are becoming more sophisticated and numerous, especially in cancer, which means there is more competition for qualified study subjects and locations. These elements are influencing

the life sciences sector's fiercely competitive environment. (DeHaas, Main, 2018) Currently, 474,085 studies have been conducted as of 2023. Among these clinical investigations, several are active, not recruiting - 19,366, completed- 257,491, and a few studies are terminated - 27,346. (Askin *et al.,* 2023)

By assessing predetermined endpoints in trial participants, such as diagnostic biomarkers, researchers can determine the efficacy and safety of a novel intervention. Only after receiving regulatory authority clearance and having the pre-clinical regulatory application reviewed by an ethical committee clinical trial can begin. (Dhudum, Ganeshpurkar, Pawar, 2024) The fundamental premise of clinical research is that researchers would generalize the findings to a wider patient population using data from a relatively small but representative sample of participants. The result's ability

to be broadly applied is hampered by a sample that is either poorly chosen or too restricted. This raises ethical and medical issues in addition to statistical ones. (Askr *et al.,* 2023)

The linear and sequential procedure used to evaluate the efficacy and safety of pharmaceuticals has not changed significantly over the previous several decades; nowadays, it takes 10–12 years on average to bring a new drug to market. Currently, drug discovery, the first stage of R&D, takes five to six years. Clinical trials then take another five to seven years. (Singh *et al.,* 2023) Only ten of the 10,000 potential medications that were initially identified are tested in clinical trials. Only one medication candidate is typically authorized for usage with patients out of the ten that are submitted for clinical trials as depicted in Figure 1. (Harrer *et al*., 2019)
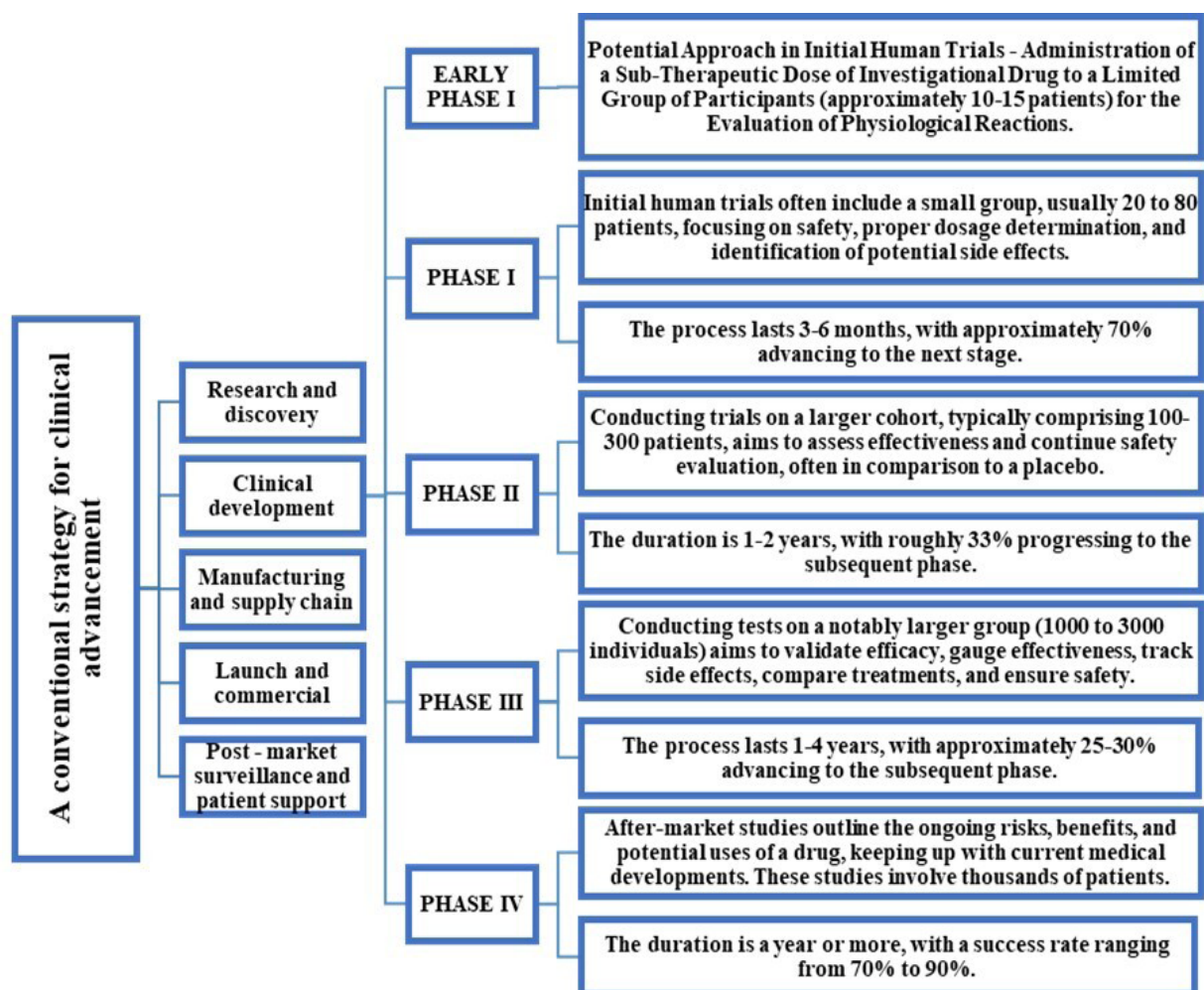

FIGURE 1 - Reinterpretation of conventional methods for conducting clinical trials.

Patients are negatively impacted by clinical trials' exorbitant costs, delays, and failures. Two-thirds of categorized disorders still lack an efficient pharmacological treatment despite multiple advancements. Therefore, it is crucial to identify better, more successful techniques to carry out clinical studies. In contrast to clinical development, drug discovery has seen a greater use of AI. This is primarily because drug research bypasses regulatory barriers by optimizing and validating prospective new medications using *in vivo* cell assays and animal models instead of testing them on humans. Academic institutions, biopharma corporations, CROs, and smaller biotech start-ups are starting to realize the potential of AI to alter clinical trials, though. (Cascini *et al.,* 2022)

Over the next few years, the biopharmaceutical industry is expected to undergo significant changes. Here are some recent developments:

- **Real-world evidence:** RWE is gaining recognition as a valuable tool for drug development and indication expansion. It is no longer limited to randomized controlled trials (RCTs) as regulators are now open to considering evidence from a variety of sources. Nearly one-third of new drug applications and biologic license applications in 2019 included RWE as supportive evidence. (Vaghela *et al.*, 2024). RWE is derived from real-world data (RWD), which is collected from a range of sources such as electronic health records, claims, and patient-generated data from in-home settings and mobile devices. This type of evidence, gathered from sources outside of traditional clinical trials, provides useful information that complements the results from these trials and addresses potential knowledge gaps about how a medication is used. RWE offers a valuable approach for enhancing Phase III registration trial data, gaining a deeper understanding of the patient experience, and evaluating the safety and effectiveness of drugs across various therapeutic areas. This type of evidence provides valuable insights into drug efficacy, safety, and usage patterns in a real-world setting. It differs from evidence obtained through randomized controlled trials (RCTs), which are typically conducted in controlled settings and only involve specific populations based on strict inclusion and exclusion criteria, to accurately measure treatment effectiveness. While RCTs have a predetermined structure and follow a uniform treatment protocol among a uniform study group, RWE, and RCTs are complementary methods that can be used together to generate robust evidence in clinical research. Decentralized clinical trials (DCTs) and hybrid trials are becoming more popular, even as the world returns to a "new normal" after the pandemic. DCTs and hybrid trials offer opportunities to collect data more widely and efficiently, and organizations are adopting new technologies to overcome challenges in recruitment and trial efficiency. (Kim *et al*., 2023). As the world moves towards a "new normal" post-pandemic, we are witnessing a rise in the popularity of decentralized clinical trials (DCTs) and hybrid trials. These innovative methods allow for more extensive and efficient data collection, and organizations are swiftly incorporating new technologies to overcome obstacles in participant recruitment and trial efficiency. According to recent research, the majority about 62% of biopharma and biotech leaders are already utilizing digital tools like cloud computing, APIs, and digital platforms in their trial operations. The use of digitalization holds great potential in addressing the hurdles of patient recruitment and retention, allowing organizations to reach previously unreachable populations. As more digital tools are developed, they will facilitate necessary changes and ensure compliance with regulatory guidelines. The adoption of virtual clinical trials is expected to enhance patient engagement, expedite clinical development timelines, and address a significant hurdle in biopharmaceutical R&D. Deloitte's research suggests that a substantial portion of trials- potentially up to half could transition to virtual formats. The digitization of patient medical information will allow for the powerful utilization of RWE. Biopharmaceutical companies are showing great interest in leveraging digital healthcare to remotely oversee their clinical trials. Novartis,

for instance, is taking steps to optimize its R&D expenses by implementing a unified 'control tower' called Nerve Live. This platform utilizes machine learning and predictive algorithms to identify potential future hurdles in clinical trials, enabling proactive intervention to prevent delays.

- **Real-world data:** RWD is becoming increasingly important in healthcare decision-making because it can produce significant perspectives that enhance the decision-making process in healthcare. RWD is collected from sources other than traditional clinical trials, such as shown in Figure 2. There has been a significant build-up of RWD as a result of the quick rise in the use of technology in healthcare, including biosensors, mobile,

wearable, and electronic systems. However, compared to data gathered during randomized controlled trials (RCTs), RWD is frequently enormous and unstructured, making gathering, storing, and analyzing such large volumes of data difficult. In addition to allowing the evaluation of RWD to produce real-world evidence (RWE), recent advancements in healthcare technology, such as linked devices, analytical techniques, and artificial intelligence (AI) technologies, can assist in partially addressing data-related issues. RWE can offer important information about the effectiveness, safety, and consumption patterns of medications and medical supplies. Figure 3 shows the use of RWD and RWE in health care.

FIGURE 2 - RWD collects data from sources other than traditional clinical trials.
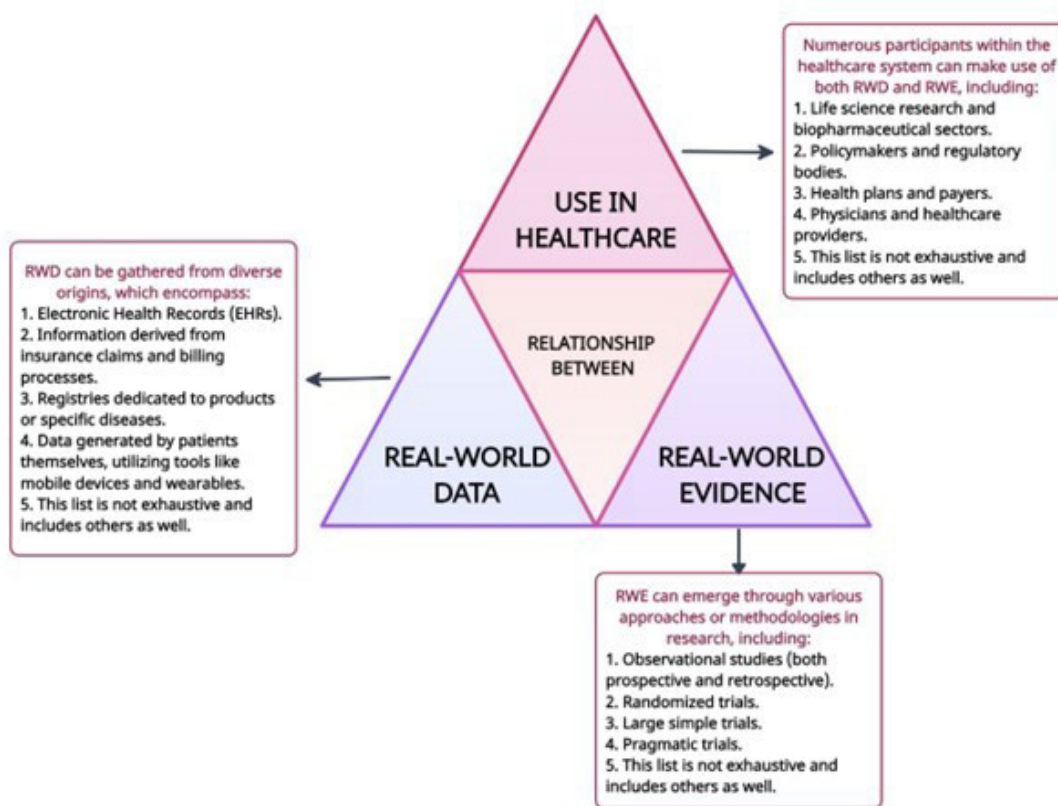
FIGURE 3 - Relationship between RWD and RWE and its use in healthcare.

Revamping clinical trials is essential for enhancing efficiency and primary hurdles in clinical development

The tried-and-true method of discrete and defined phases in randomized controlled trials (RCTs) was created primarily for evaluating products for the mass market. RCTs, on the other hand, lack the analytical strength, adaptability, and speed needed to create sophisticated novel treatments that focus on more specialized and frequently diverse patient groups. Additionally, clinical development is having trouble keeping up with the rapid expansion of genetic knowledge, RWE, and other new data sources such as biosensors. (Subbiah, 2023).

From discovery through launch, an asset's average development cost has gone up. The corporations under study invested $139 billion in R&D in 2022, which represents a 2% decline in core R&D spending from 2021 i.e. $141 billion. The average cycle time duration is lengthening, which is the major cause of the rise in 2022 compared to 2021. The COVID-19 effect on cycle time acceleration that was predicted last year has not persisted. From a range of $4,239 million (highest cost: $5047 million, lowest cost: $808 million) to $5,437 million (highest cost: $6716 million, lowest cost: $739 million), the expenses to construct an asset have grown in comparison to 2021. The key factors influencing R&D success include the lengthening of clinical development or cycle timeframes, modifications to drug delivery systems, and innovation-generating sources. Specifically:

• The most urgent issue facing clinical development is undoubtedly the lengthening clinical trial cycle.
• Historically, firms have concentrated mostly on tiny compounds, but during the past ten years, the percentage of larger, more complicated biological molecules has increased in the firm's pipelines.
• Partnerships, mergers, and acquisitions are becoming more and more of a source of innovation.

The establishment of a clinical protocol (a written document outlining the trial's procedures and ensuring participant security and data integrity) is the first stage in the clinical research process. The accessibility of a rising quantity, and diversity of information, along with the patient-reported outcome data, genomics, imaging, and digital health, has prompted an extension of trial procedures to satisfy strict regulatory requirements. Companies have also reported having a harder issue finding patients who fit the trial selection requirements. Additionally, the rivalry for patients is rising as a result of the novel paradigm being used in drug development, which complicates recruiting. The typical length of clinical trials has grown as a result of these considerations. Particularly, as clinical studies advance, more participants are needed, but the eligibility and suitability standards also rise. Patient's health history or inconsistency between their illness stage and the research procedure may exclude them from taking part. Patients who are eligible and suitable can find the prerequisites difficult or the recruiting procedure difficult and time-consuming, or they might not be aware of or motivated to join.

Despite the complexity of clinical trials, one of the major obstacles to their success isn't related to medical or regulatory issues; instead, it often involves the ability of research sites to recruit and retain a sufficient number of patients for the entire duration of the study. Difficulty in enrolling participants can lead to costly delays or even the premature termination of the trial. Almost 80% of clinical trials fail to meet their initial enrolment deadlines, and approximately 55% of trials are prematurely terminated due to an inability to reach full enrolment. There are various reasons why clinical trial sites struggle to meet their recruitment targets, and these include financial barriers, logistical concerns, and the lack of research support some of the main issues are which impact the sites are shown graphically in Figure 4. (Briel *et al.*, 2021).
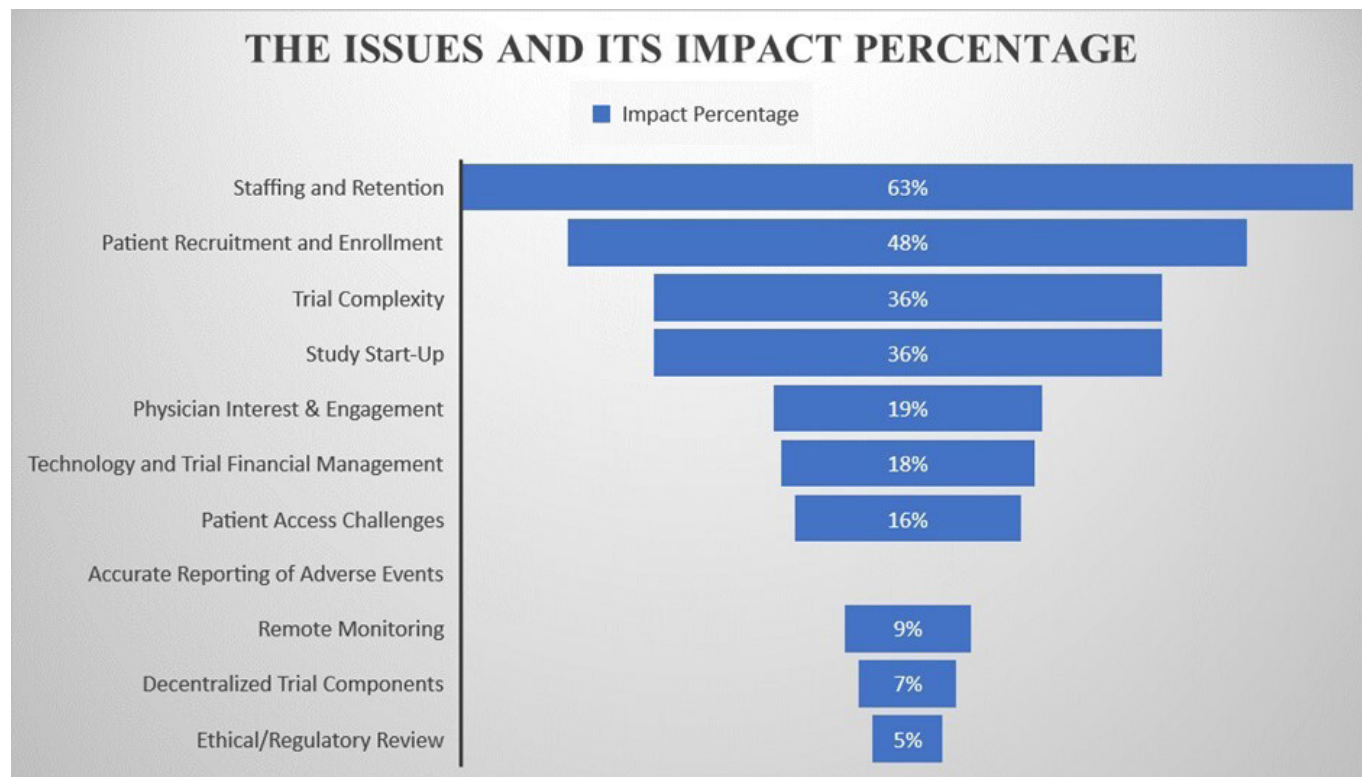

FIGURE 4 - Major issues which impact sites and its impact percentage.

According to recent research, the primary variables impacting clinical trial expenses include the development of experimental drugs, patient identification and recruitment, patient retention and engagement, and data management. Utilizing less costly facilities and in-home testing can reduce per-trial costs by as much as 16% in Phase 1, 22% in Phase 2, and 17% in Phase 3, depending on the therapeutic area. (Williams *et al.,* 2023) Public health is greatly affected by the growing cost of clinical research since it deters pharmaceutical companies from doing clinical trials. The forecasted medical expense trend for 2024 is 7.0%, which is higher than the 5.5% and 6.0% projected trends for 2022 and 2023, respectively. The following Table I summarises the cost drivers and their percentage effect. It is important to note that the specific clinical trial and therapeutic area may have an impact on the cost drivers' percentage impact. (Goel *et al.,* 2017) (Winkfield *et al.,* 2018).

TABLE I - Cost drivers in Clinical trials

Cost Driver	Percentage Impact
Investigational product manufacturing	N/A
Patient identification and recruitment	1.7% to 2.7% of total trial budget
Patient retention and engagement	N/A
Data management	N/A
Use of lower-cost facilities and in-home testing	Up to 16% in Phase 1, up to 22% in Phase 2, and up to 17% in Phase 3, depending on therapeutic area

Finding eligible individuals who meet the criteria helps speed up clinical studies, increase their effectiveness, and eventually hasten the approval and distribution of new medications. However, statistics reveal that only a tiny proportion of eligible people take part in clinical trials. For instance, about 2–9% of adult carcinoma-suffering patients take part in clinical studies. Only 8.1% of potential patients got involved in clinical trials, according to a meta-analysis of 13 studies involving 8,883 patients.

Of those who didn't, around 55.6% didn't have access to trials where they were receiving treatment, 21.5% were considered ineligible, and 14.8% declined to register in a trial that was open to them. (Unger *et al.,* 2021).

The patient group that a novel drug is anticipated to treat and those taking part in the associated clinical study are also at odds with one another. Raising clinical trial variety in a way that is efficient, scalable, and sustainable continues to be a problem for clinical research despite

several attempts to address it. (Clark *et al.*, 2019). Patients who are thinking about taking part in a clinical trial of a new drug must also assess the advantages of early access to a prospective novel medication versus the potential danger, discomfort, economic load, and time commitments. Clinical trials often encounter challenges such as undesirable site preferences, poor research design, unsatisfactory trial operation, security concerns, and dropouts owing to logistical concerns. (Fogel, 2018). The four-fifths of studies are unsuccessful because they are unable to show efficacy or safety, even when patient recruitment and retention increase the length of time needed to finish a study. (Dowden, Munro, 2019).

Additionally, each phase of a study requires more time and money to accomplish it. The expense of all earlier stages as well as the amount of time that could have been spent testing a new medicine are included in the overall cost of a Phase III failure. Each unsuccessful study adds to the escalating price of biopharmaceutical R&D (Mullard, 2018).

Creative approaches to accelerate clinical trial timelines

In recent years, several novel methods in clinical trial design have arisen that make better use of data from various sources to shorten clinical cycle timeframes, comprise the following:

Adaptive clinical trials: Adaptive Clinical trials allow for ongoing trial design adjustment in response to interim results. This can increase the chance of success while requiring less time and money. (Kaizer, 2023). Expanding the use of adaptive trials might get rid of a lot of unexpected dangers that weaken effective medications and protract development periods needlessly. For instance, adaptive techniques can give trial dose information in a single combined Phase II/III study lasting two years, as opposed to the three or more sequential traditional trials that might take place over a longer period. By employing the same patients at more than one stage, such seamless trials might decrease the overall sample size required while also speeding up the development process. Other benefits include adjusting allocation rates, stopping the study early, and re-evaluating particular therapies, all of which increase efficiency. (Ciolino, Kaizer, Bonner, 2023).

Master protocols: Multiple experimental drugs are evaluated concurrently within the same general trial framework using master protocols. (Park *et al.,* 2019). Using master protocols, biopharma organizations may safeguard R&D activities, enhance the standard of the research, and lower expenditure and study timelines, according to a paper from the Deloitte US Centre for Health Solutions. Estimated expenses for a Phase II oncology trial might be decreased by 12–15%, and the study period could be shortened by 13–18% by 15–21 weeks. (Bogin, 2020).

Synthetic control arms: RWE is used in synthetic control arms in a more practical, secure, duration- and money-efficient method of conducting studies, particularly those with limited numbers of possible participants. Currently, one of the main reasons people decide not to take part in scientific studies is fear of receiving a placebo. Data from EHRs, patient-generated information from activity trackers/medical devices, ailments documents, and other sources is being gathered for a synthetic control arm. These data are then utilized to replicate or model the anticipated outcomes and compare them to those from the clinical study. All participants get the active therapy, allaying worries regarding treatment assignment, when the typical control arms are eliminated or reduced. Synthetic control arms improve efficiency, cut down on delays, and lessen trial costs. Additionally, their use reduces the possibility of unblinding, which occurs when patients learn which therapy, they are receiving and compromises the validity of the experiment. (Thorlund *et al.,* 2020). Pharmacogenetics testing -testing for pharmacogenetics to choose patients. The use of selected pharmacogenetic biomarkers for selecting patients to determine each person's reaction to medications in terms of effectiveness and safety was present in more than half of all studies i.e. 55% that were started in 2018. Compared to clinical studies without the use of biomarkers, the success rate of these trials was four times higher.

The influence of artificial intelligence on the clinical trial procedure

AI refers to a range of computer programs and systems that can perform tasks that mimic human

intelligence. These technologies include computer vision, deep learning, machine learning, natural language processing, robotics, speech recognition, supervised learning, and unsupervised learning, Figure 5 shows the major components of AI. AI can derive insights and connections from data, learning autonomously from patterns within the data. This enables machines to accomplish tasks that we typically associate with human intelligence, extending human capabilities. AI comes in different forms that have become widely available in everyday life, such as smart speakers with voice assistants, AI chatbots, and recommendation systems. The ability to easily automate tasks is the biggest quality that sets AI aside from other computer science topics. (Haleem *et al.,* 2023).
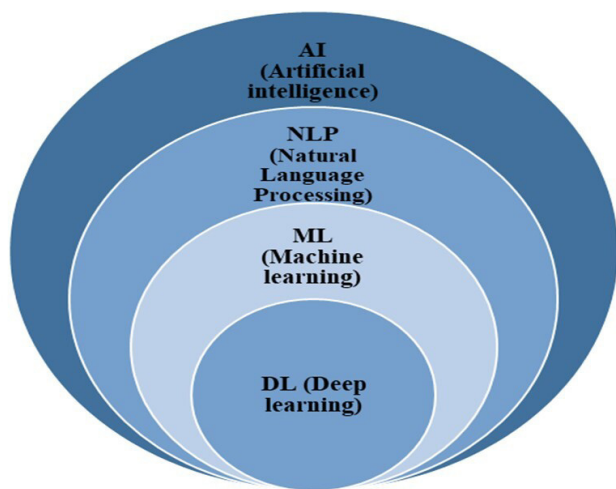

FIGURE 5 - Major components of AI.

Deep learning (DL), machine learning (ML), and natural language processing (NLP), in particular, have the potential to enhance drug acceptance rates, lower process costs, and speed up the delivery of medical supplies to patients when paired with an efficient digital infrastructure. RWD, sometimes referred to as scientific and research data, is becoming available to biopharmaceutical firms from several sources. Unlocking RWD with predictive AI models and analytics tools can expedite the comprehension of medical disorders, identify suitable subjects and principal investigators to guide site selection including virtual trials, and facilitate novel clinical research designs. Integrating artificial intelligence

into operational data can improve clinical trial efficiency. Therefore, implementing AI technology is turning into a crucial corporate requirement. Selection of patients and sites, patient enrolment and retention procedures, also the absence of adequate facilities to handle the complexity of operating a clinical study, are key factors that undermine the success of clinical trials. This is particularly difficult in the later stages, where effective and trustworthy compliance measures, endpoint identification, and patient surveillance systems are required.

According to market estimations, the AI-based clinical trials industry is expected to reach a market size of USD 5.43 billion in 2022. Over time it is projected to experience growth and reach a valuation of, around USD 11.86 billion by the year 2030 with an annual growth rate of about 10.26%. Looking specifically at the United States AI-based Clinical Trials Solution Provider market it is estimated to have a worth of US$ 600 Mn in 2022. Is projected to achieve a valuation of around US$ 5.7 Bn by the year 2032. The market size of AI-based clinical trial solution providers is expected to grow at a CAGR of 21.5% from 2023 to 2031. The global artificial intelligence (AI) in life sciences market size was exhibited at USD 1.43 billion in 2022 and is projected to hit USD 8.92 BN by 2032. As per TBRC's market forecast, the AI in clinical trials market size is predicted to reach $18.83 billion in 2027 at a CAGR of 41.20%. (Biospace, 2023) (Lifesciencesintelligence, 2023)

Leading the application of AI and digital technology in clinical trials are several biopharma organizations and a few of these organizations are listed in Table II. Saama, ConcertAI, and BenevolentAI are just a few of the significant AI businesses in the clinical research sector. One of the most advantageous applications of AI is in clinical trial design, patient recruitment and stratification, regulatory filing optimization, and clinical trial outcome prediction. Additionally, there is a rising interest in and acceptance of AI-based clinical trial solutions from academic institutions, pharmaceutical and biotech businesses, and contract research organizations (CROs). AI-based solutions are now being used in more clinical trials. (Visiongain Reports Ltd, 2023). Various AI and digital technologies are being used in clinical trials by biopharma businesses. Among these technologies are:

- AI-powered algorithms for clinical trial design and optimization. (Zhang, 2023; Us, 2024; Aung, Wong, Ting, 2021)
- Wearable devices, remote monitoring, and virtual clinical visits to expand patient access to trials. (Mitsi *et al.*, 2022).
- AI tools for drug discovery and identifying drug development targets. (Qureshi *et al.*, 2023).

- Digital mobile health applications, external, wearable, implantable, and ingestible devices or sensors for data collection. (Mukherjee *et al.*, 2022).
- AI for patient recruitment and retention
- AI for analyzing trial results and real-world evidence. (Firth *et al.*, 2020).
- AI for automating processes to increase the speed and efficiency of results publication

TABLE II - List of biopharma organizations that use only RWD and both AI and RWD in clinical trials

BIOPHARMACEUTICAL ORGANIZATION	NUMBER OF TRIALS CONDUCTED USING RWD	NUMBER OF TRIALS CONDUCTED USING AI AND RWD
Massive Bio	1	1
AstraZeneca	88	3
Takeda	40	1
Pfizer	85	-
Sanofi	22	-
Novartis	52	3
Roche	24	3
Johnson & Johnson	7	1
GSK	28	-
Merck & Co	1	-
Bristol Myers Squibb	26	-
Bayer	59	2
Lilly	7	-
Merck	24	-
Astellas Pharma	6	-

These technologies are being utilized to increase the quantity of objective data gathered, the productivity, and cost-effectiveness of clinical trials, as well as to enhance patient outcomes. Biopharma firms use a variety of important measures, such as clinical trial success rate, patient recruitment and retention, regulatory compliance, efficiency, and cost savings, to assess the effectiveness of AI and digital technology adoption in clinical trials as depicted in Figure 6.
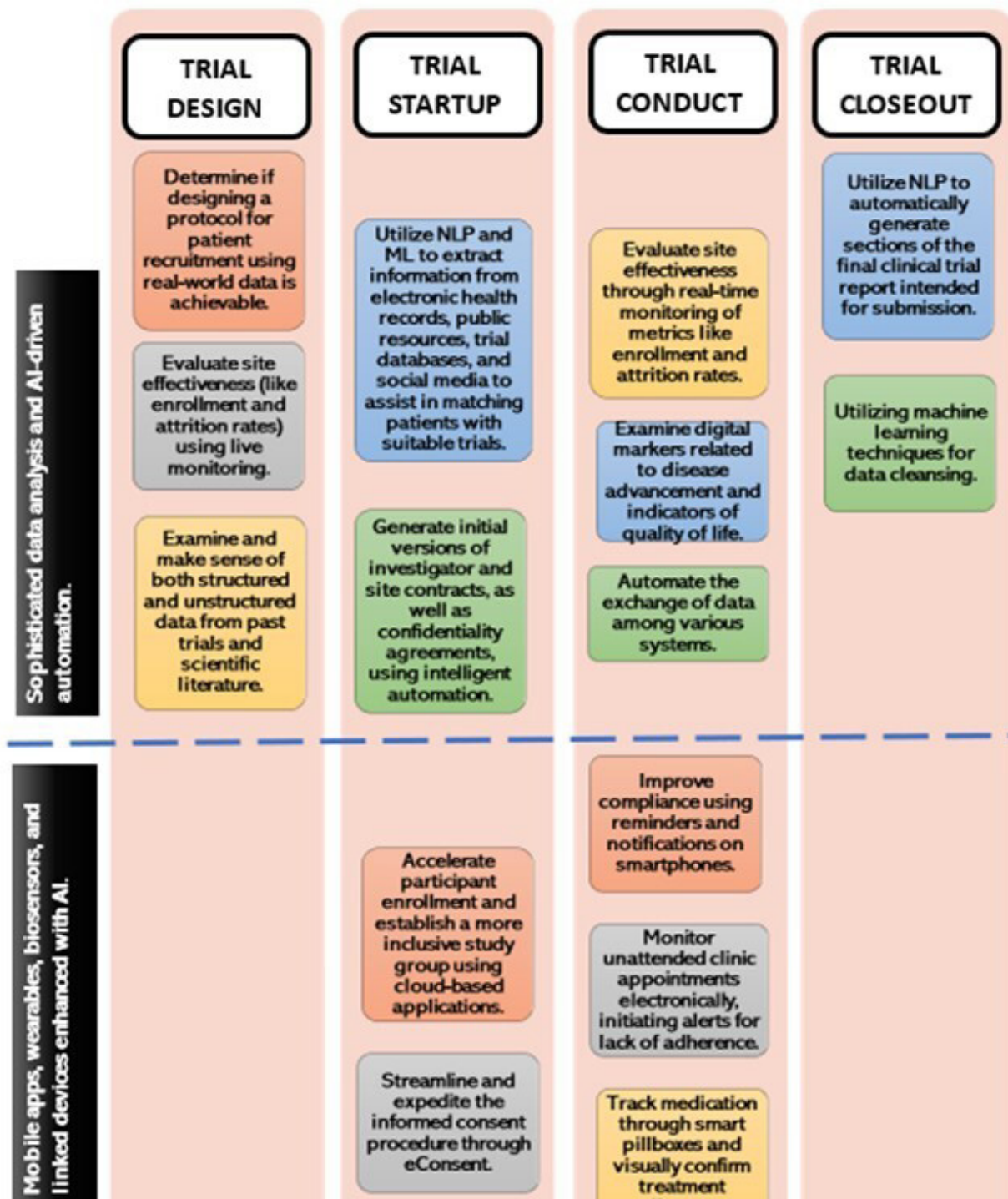
TRIAL DESIGN

TRIAL STARTUP

TRIAL CONDUCT

TRIAL CLOSEOUT

Sophisticated data analysis and AI-driven automation.

Determine if designing a protocol for patient recruitment using real-world data is achievable.

Evaluate site effectiveness (like enrollment and attrition rates) using live monitoring.

Examine and make sense of both structured and unstructured data from past trials and scientific literature.

Utilize NLP and ML to extract information from electronic health records, public resources, trial databases, and social media to assist in matching patients with suitable trials.

Generate initial versions of investigator and site contracts, as well as confidentiality agreements, using intelligent automation.

Evaluate site effectiveness through real-time monitoring of metrics like enrollment and attrition rates.

Examine digital markers related to disease advancement and indicators of quality of life.

Automate the exchange of data among various systems.

Utilize NLP to automatically generate sections of the final clinical trial report intended for submission.

Utilizing machine learning techniques for data cleansing.

Mobile apps, wearables, biosensors, and linked devices enhanced with AI.

Accelerate participant enrollment and establish a more inclusive study group using cloud-based applications.

Streamline and expedite the informed consent procedure through eConsent.

Improve compliance using reminders and notifications on smartphones.

Monitor unattended clinic appointments electronically, initiating alerts for lack of adherence.

Track medication through smart pillboxes and visually confirm treatment

FIGURE 6 - AI and digital technology adoption in clinical trials.

Reinventing Planning and Execution of Clinical Studies

As discussed in the initial section of this report, biopharmaceutical firms are embracing diverse approaches to bring innovation to clinical trials. These strategies hinge on leveraging a growing volume of scientific and research data originating from various sources. These sources encompass present and prior clinical studies, patient assistance programs, and post-

market supervision. Collaborations with academic institutions, hospitals, and technology firms can provide access to additional data. Study investigators must examine the PICOTS aspects so that it would be helpful for the cofounders to legitimately answer a specific scientific issue at hand within a certain RWD source. In evidence-based practice and research, the PICOTS model is frequently utilized to organize clinical research questions and direct the creation of systematic reviews. It assists in making sure that every pertinent facet of a research project or intervention is taken into account. The components of PICOTS aspects are described in Figure 7.
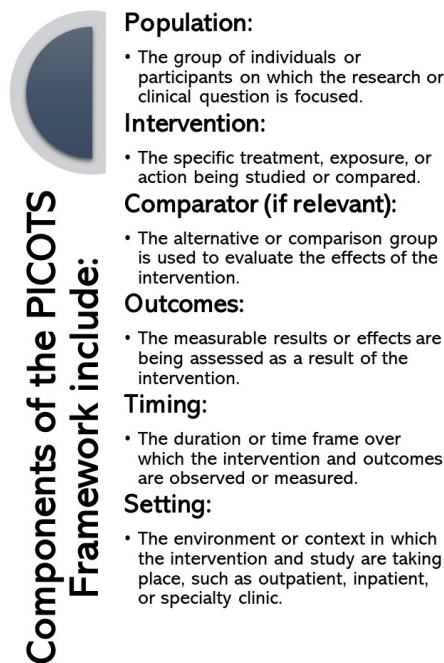

Components of the PICOTS Framework include:

Population:
- The group of individuals or participants on which the research or clinical question is focused.

Intervention:
- The specific treatment, exposure, or action being studied or compared.

Comparator (if relevant):
- The alternative or comparison group is used to evaluate the effects of the intervention.

Outcomes:
- The measurable results or effects are being assessed as a result of the intervention.

Timing:
- The duration or time frame over which the intervention and outcomes are observed or measured.

Setting:
- The environment or context in which the intervention and study are taking place, such as outpatient, inpatient, or specialty clinic.

FIGURE 7 - Components of PICOTS model.

Employing AI on RWD holds the potential to extract meaningful insights and patterns, thus enhancing the design of clinical studies. AI can enhance the accuracy and efficiency of collecting and analyzing biomarker data at predetermined intervals, surpassing current patient-initiated self-monitoring techniques. Furthermore, AI-powered technologies possess unparalleled capabilities in sorting and analyzing the expanding pool of data amassed through biopharmaceutical research and development. For instance, historical trial data, including unsuccessful ones, can be harnessed to enhance future trial designs.

AI's application also streamlines the continuous flow of RWD by swiftly organizing, consolidating, coding, storing, and managing it. This accelerates the process of data management, making it more seamless and dynamic.

Enhancing Patient Selection, Recruitment, and Enrolment

The integration of AI-driven digital transformation can mitigate challenges associated with patient selection by utilizing clinical trial enrichment approaches are represented in Figure 8. The FDA has issued guidelines on employing these approaches, aiding the evaluation of human drugs and biological products effectiveness. (Ionan *et al.*, 2023). These strategies, combined with AI implementation, encompass the following approaches:

- *Reduced Population Heterogeneity:* This involves selecting patients with disease baseline measurements or biomarkers that closely define the disease within a narrow range. Simultaneously, patients with spontaneous symptom improvement or highly variable measurements are excluded to enhance study power. Electronic phenotyping, a process that minimizes population heterogeneity, is commonly employed. AI technologies, specifically Machine Learning (ML) and Deep Learning (DL), are harnessed to expedite patient identification for clinical trials through electronic phenotyping. (Banda *et al.*, 2018).

- *Prognostic Enrichment:* This strategy focuses on choosing patients with a higher probability of experiencing disease-related endpoints or significant deterioration in their condition (for continuous measurement endpoints). AI has substantial applications in prognostic enrichment, particularly in neurological diseases. By combining cost-effective and non-invasive models, AI approximates complex biomarkers that are otherwise expensive or invasive to measure.

Predictive Enrichment: Predictive enrichment entails selecting a patient population who are likely to respond positively to the drug therapy compared to others with the same condition. This approach can yield

larger effect sizes and permit the use of smaller study participants. Selection of patients can be grounded in patient physiology, biomarkers, or disease characteristics linked to the study drug's mechanism. Complex ML models are employed in predictive enrichment to assess disease progression, particularly in diseases like Alzheimer's disease, where disease-modifying drugs are limited. (Liu, Panagiotakos, 2022)

The European Medicines Agency (EMA) also proposes collaborative efforts to innovate and expedite patient identification in clinical trials. This includes partnering with international stakeholders on initiatives like the Clinical Trial Transformation Initiative (CTTI), aligning with the Regulatory Science to 2025 strategy. (Liu *et al.*, 2021).
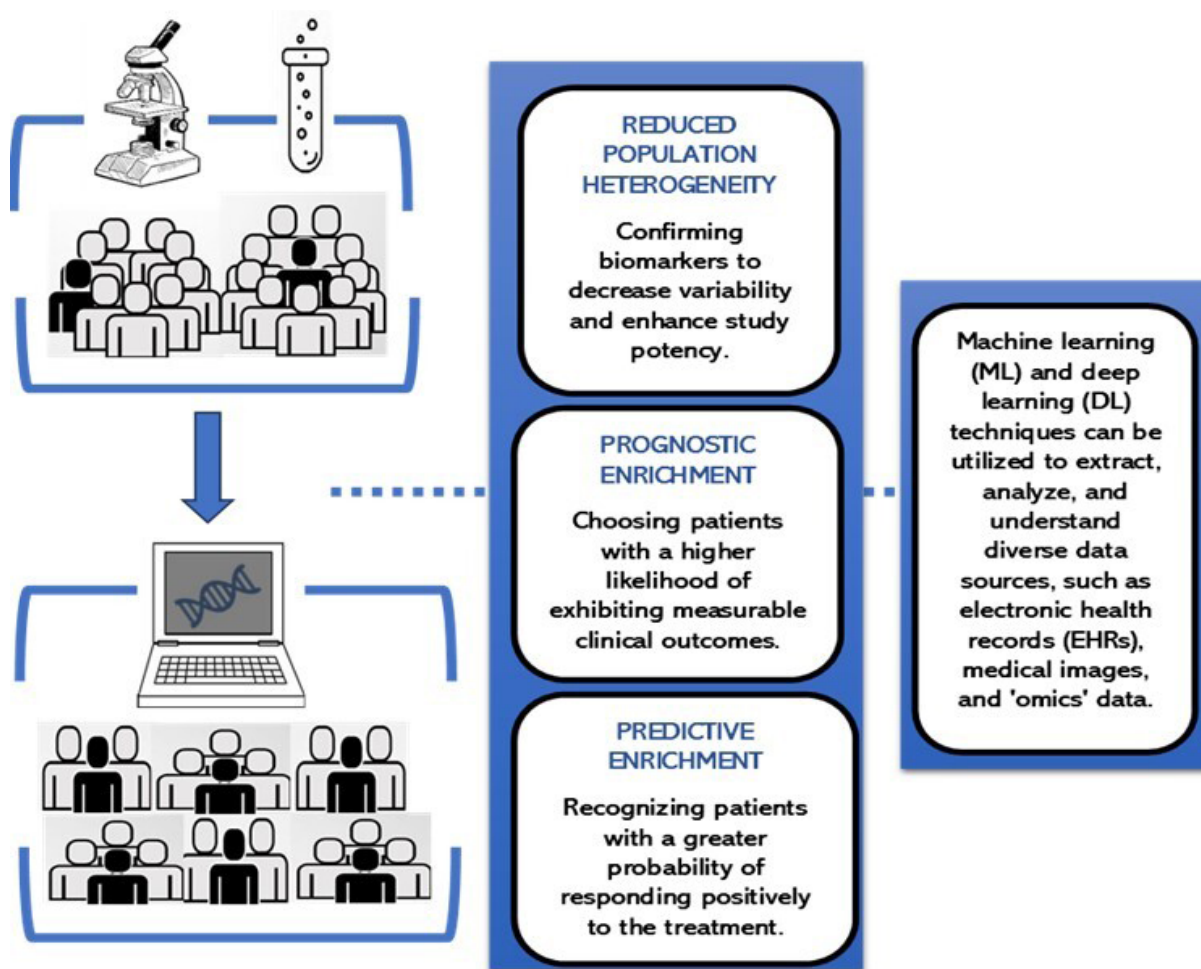
FIGURE 8 - Clinical trial advancement techniques can be delivered with the use of AI technology.

Extracting Insights from Publicly Accessible Data

Utilizing publicly accessible data, Machine Learning (ML) and Natural Language Processing (NLP) technologies can proactively extract information from sources such as digital trial announcements, trial databases, and social media. This information can be employed to facilitate the alignment of patients with suitable clinical trials. AI-driven clinical trial matching systems, exemplified by solutions like IBM Watson for Clinical Trial Matching, play a role in alleviating the challenges associated with recruitment and enrolment.

A state-of-the-art tool that uses artificial intelligence (AI) to expedite the clinical trial matching process is IBM Watson Health's Watson for Clinical Trial Matching (CTM). CTM can improve the precision and effectiveness of clinical trial matching by evaluating structured and unstructured data from a variety of sources, including Electronic Health Records (EHRs), medical literature, trial information, and eligibility requirements from open databases like ClinicalTrials.gov. An EHR includes the following data as per the Table III. Among IBM Watson Health's CTM's salient features are:

- Examining information from many sources, including EHRs, journals, and trial data;
- Determining trial inclusion and exclusion standards that restrict participation

- Deciding which patient demographics at trial locations are viable
- Correlating organized and unstructured patient data from EHRs

Within 11 months of its introduction in cooperation with the Mayo Clinic, the early usage of CTM increased enrollment in clinical trials for systemic treatment for breast cancer by 80%. In addition, the system is being investigated further for new applications including radiation, surgery, and supportive care, as well as other cancer types like lung and gastrointestinal malignancies. In a different partnership, Novartis, Highlands Oncology Group, and IBM Watson Health processed ninety patients against three breast cancer protocols in twenty-four minutes using the CTM system, as opposed to an hour and fifty minutes for a clinical trial coordinator i.e., a 78%time savings.

TABLE III - Data included in Electronic Health Record

General Structure of Electronic Health Record	Data included
Inpatient Hospitalization	• Diagnoses • Procedures • Medication administration • Clinical notes*
Emergency Room	• Diagnoses • Procedures • Medication administration • Clinical notes*
Primary Care Visit	• Diagnoses • Procedures • Medication administration • Clinical notes*
Specialist Clinic Visit	• Diagnoses • Procedures • Medication prescription • Clinical notes*
Pharmacy	• Medication dispensing • Clinical notes*
Imaging	• Procedures • Results • Clinical notes*
Laboratory	• Procedures • Laboratory results • Clinical notes*
	Clinical notes* (could include personal and clinical details such as height, weight, age, race/ethnicity)

Selection of Investigators and Sites

Selection of proficient investigator sites is a pivotal aspect of clinical trials. These sites' qualities which include collaborative relationships, professional expertise, administrative processes, and resource availability have a big impact on research schedules, accuracy of data, and effectiveness. The impact of the selection of a site on product approval, study expenses, and timelines is substantial, yet this domain is often undervalued and inadequately comprehended. Furthermore, investigators and sites are required to enter into formal agreements that ensure compliance with GCP regulations and approved protocols. This entails adherence to procedures for auditing, accommodating monitoring schedules, and securing crucial documents as per sponsor mandates.

AI technologies offer the potential to enhance the identification of target locations, qualified investigators, and priority candidates with precision. These technologies also streamline data analysis and facilitate the automation of workflows through the generation of standardized contracts such as confidentiality agreements and investigator-site agreements. This, in turn, reduces the time required for study start-up.

Monitoring Patients, Ensuring Medication Adherence, and Maintaining Participation

In terms of patient monitoring, medication adherence, and retention, algorithms play a significant role by automating data collection, digitizing regular clinical assessments, and facilitating data sharing across various systems. AI solutions can assist nurses and physicians in identifying pertinent actions aligned with protocol requirements, including specific clinical tests and procedures for monitoring diagnostic biomarkers. These solutions can aid in patient appointment scheduling and entering individual patient information into Electronic Data Capture systems. For instance, Natural Language Processing (NLP) can fill sections of submission dossiers to prepopulate essential information into the final clinical study report. Such applications lead to cost and time savings, reduced compliance risks, and expedited time-to-market. Clinical trials necessitate a sufficient number of participants to achieve statistical power for assessing a drug's effectiveness. Ensuring patient retention and adherence post-recruitment is crucial to prevent trial delays and added expenses. Replacing patients who drop out is not straightforward due to statistical requirements. For instance, a 20% decrease in adherence necessitates a 50%increase in sample size to maintain statistical power. Despite this, the average withdrawal rate in clinical trials stands at 30%, with only 15% of trials experiencing no patient attrition. (Deng, Hsu, Shyr, 2023)

Typically, researchers have limited insights into patient health beyond site visits during trials, making accurate assessment of treatment protocol compliance challenging. This mismatch can lead to disparities between treatment efficacy in trials and real-world drug effects. Advanced AI algorithms, drawing on data collected via digital gadgets from trial participants offer immediate perspectives on the effectiveness and security of treatments. AI can amalgamate various digital biomarkers to comprehend patient responses to drugs, facilitating dose adjustments when necessary. Importantly, these interconnected apps and devices provide patients with real-time information and support, thereby enhancing engagement and retention. (Santos *et al*., 2022). The FDA has approved several AI-augmented platforms for remote patient monitoring, suitable for both healthcare and clinical trials. Additional adherence-improvement technologies include smart pillboxes, virtual pillboxes, and incentives grounded in behavioral economics. (Shahani *et al*., 2022) Deep Learning (DL) and Machine Learning (ML) algorithms can analyze real-time patient data from wearables and video monitoring, predicting individual patient dropout risks by detecting behavior patterns that previously led to failure to comply.

Leveraging operational data for AI-powered clinical trial analytics

In the realm of clinical trials, copious operational data is generated. However, the presence of functional data silos and a multitude of applications often pose challenges for biopharma executives seeking a holistic perspective of their broad clinical study repertoire

across different centers. This impedes their ability to make informed decisions. As a result, a great deal of effort is put into gathering and evaluating a variety of datasets to improve trial activities and maximize cost and resource efficiency. A promising strategy to address this entails centralizing managerial information on a clinical study analytics system equipped with predictive capabilities. This empowers biopharma firms to better differentiate true risks from data anomalies, leading to more efficient and productive visits. (Lehne *et al.*, 2019) Issues concerning IT infrastructure and data interoperability are also prevalent, particularly regarding standardizing data sharing across various Electronic Data Capture (EDC) systems and sites, including access to Electronic Health Records (EHRs). Some biopharma firms handle interoperability challenges by setting data management guidelines that prescribe specific data platforms and delivery methods for their studies. A viable solution involves embracing open data standards to enhance interoperability and facilitate seamless integration. An open platform approach simplifies the incorporation of data from sensors, user applications, and wearable devices through standardized application programming interfaces (APIs). (Gross *et al.*, 2022) The act of consolidating data from diverse sources onto a shared analytics platform within a company can stimulate collaboration and integration. This platform can offer insights into crucial metrics encompassing enrolment rates, screening failures, and protocol deviations.

Key enablers advancing AI role in clinical trials which brings the revolutionary shifts supporting the integration of AI into clinical trials

Within the biopharmaceutical sphere, a strategic shift is underway as companies seek to leverage outsourcing models and forge operational partnerships. An increasing number of enterprises recognize Contract Research Organizations (CROs) that have invested in data science capabilities as vital strategic allies. These CROs not only offer specialized proficiency but also provide access to a diverse pool of potential trial participants. (Yaqub, Alsabban, 2023) A subsequent study conducted in 2018 suggested that more companies would adopt outsourcing to gain expertise, particularly in cutting-edge domains such as AI, cloud computing, and robotics. This sector's expansion is driven by strategic collaborations encompassing academia, analytics firms, tech giants, and CROs. This drive toward strategic partnerships aims to bolster research and development capabilities within biopharma companies. (Rajapathirana, Hui, 2018)

CROs are playing a vital role in transforming clinical trials by offering diverse expertise to address intricate technical challenges. Research and Markets projected in 2015 that over 70% of clinical trials would be outsourced to CROs by 2020. CROs are anticipated to see increased demand as a result of their special ability to amalgamate AI technology with therapeutic specialization across indications and regulatory requirements, as AI is becoming more and more popular in the biopharmaceutical industry. Additionally, pharmacovigilance professionals are anticipated to be in higher demand from CROs. The global CRO market is expected to increase at a compound annual growth rate (CAGR) of 7.62% from $36.27 billion in 2017 to $56.34 billion in 2023, according to a 2018 Research and Markets analysis. This predicted expansion is the result of more investment in research and development more clinical trials, and an expected spike in the outsourcing of research and development operations. The major players operating in the AI-based clinical trial solution providers market include Oracle, IBM, Medidata Solutions, and Parexel. (Chaudhari *et al.*, 2020) Simultaneously, an expanding array of start-ups is emerging within the clinical trials arena, often in collaboration or partnership with biopharmaceutical entities. Some illustrative examples include:

- *Trials.ai:* It analyses large amounts of genetic data, research papers, old clinical studies, and various other analysis formats using AI to improve trial design. The system gathers data, draws conclusions, and advises trial sponsors on how to improve their study procedures using its own coded clinical trials database. Improved protocol designs lead to enhanced recruitment and retention, reduced patient and trial site burden, and ultimately cost

and time efficiency gains (Anaya-Isaza, Mera-Jimenez, Zequera-Diaz, 2021), for a particular client, Trials.ai shortened study timelines by 33% and diminished data errors by 20%. (Mehta, 2024) *Concerto HealthAI:* Leverages its Real-World Data (RWD) capabilities and eurekaHealth AI platform to formulate and create reliable clinical trial studies and establish recommendations for precision therapy. Concerto HealthAI has established strategic agreements with prominent pharmaceutical players like Bristol-Myers Squibb and Pfizer. (Terry, 2019)

- *GNS Healthcare*: Harnesses its Reverse Engineering and Forward Simulation (REFS) AI and simulation system to analyze RWD and clinical study information. This empowers the modelling of patient responses to treatments in silico. Notably, GNS Healthcare collaborates with biopharmaceutical leaders including Amgen, Bristol-Myers Squibb, and others. (Bhatt, 2019).

In the healthcare sector, the big digital companies are upending the established quo by leveraging technology to impact the life sciences industry. Here are some initiatives that highlight their involvement:

- *Verily Life Sciences:* Verily, a subsidiary of Google's Alphabet Inc., has partnered with pharmaceutical companies such as Sanofi, Novartis, Otsuka, and Pfizer on a project called Project Baseline. Verily is using AI-enabled research kits, including sensors, to gather data from electronic health records to plan to launch studies in various areas, including cardiovascular disease, dermatology, and oncology. (Rashid, 2021).*Apple:* With top research and educational establishments as partners, Apple has started three clinical investigations. Their ResearchKit app is used in these investigations. The studies consist of the Apple Heart and Movement Study in collaboration with Brigham and Women's Hospital and the American Heart Association, the Apple Women's Health Study in collaboration with Harvard T.H. Chan School of Public Health and National Institute of Environmental Health

Sciences, and the Apple Hearing Study in collaboration with the University of Michigan. Utilizing the ResearchKit app and the Apple Watch, Apple has also finished the Apple Heart Study. (Apple, 2019).

- *Amazon:* AWS Cloud NLP service Comprehend Medical, developed by Amazon, deciphers and mines both structured and unorganized information from clinical trial results, physician notes, and electronic health records. (Singh *et al.*, 2020). This service extracts information such as medical conditions and medication regimens. Amazon's AI-enabled services and tools are compliant with HIPAA and GDPR, making them suitable for streamlining clinical trials, data management, patient recruitment, and monitoring. (Bajwa *et al.*, 2021). These initiatives by tech giants are disrupting the healthcare industry by introducing advanced data science, medical knowledge, and technology to improve patient care, clinical trials, and research. They are leveraging wearable devices, AI-powered tools, and cloud services to collect and analyze health data, streamline processes, and accelerate innovation in the life sciences industry. (Aerts, Bogdan, 2021).

Microsoft and Novartis have entered into a five-year collaboration to explore how AI technology can be combined with Novartis' life sciences expertise to tackle difficulties in research, production, financing, and pharmaceutical discovery. The collaboration will concentrate on three main areas: personalized care for macular degeneration, increasing the productivity of the production of novel gene and cell treatments, and reducing the time needed to create and develop new medications. Novartis researchers will be able to leverage the power of AI to speed up the drug discovery process, which can take years, to weeks or even days. As part of the strategic partnership, Novartis is bringing AI to the desktop of every company associate, enabling citizen data scientists to embed AI-based tools into every aspect of the organization's operation. (Vora *et al.*, 2023). In fact, over the course of the next five to ten years, AI-powered apps are anticipated to grow the norms in the biopharma functioning paradigm that is present in Figure 9.
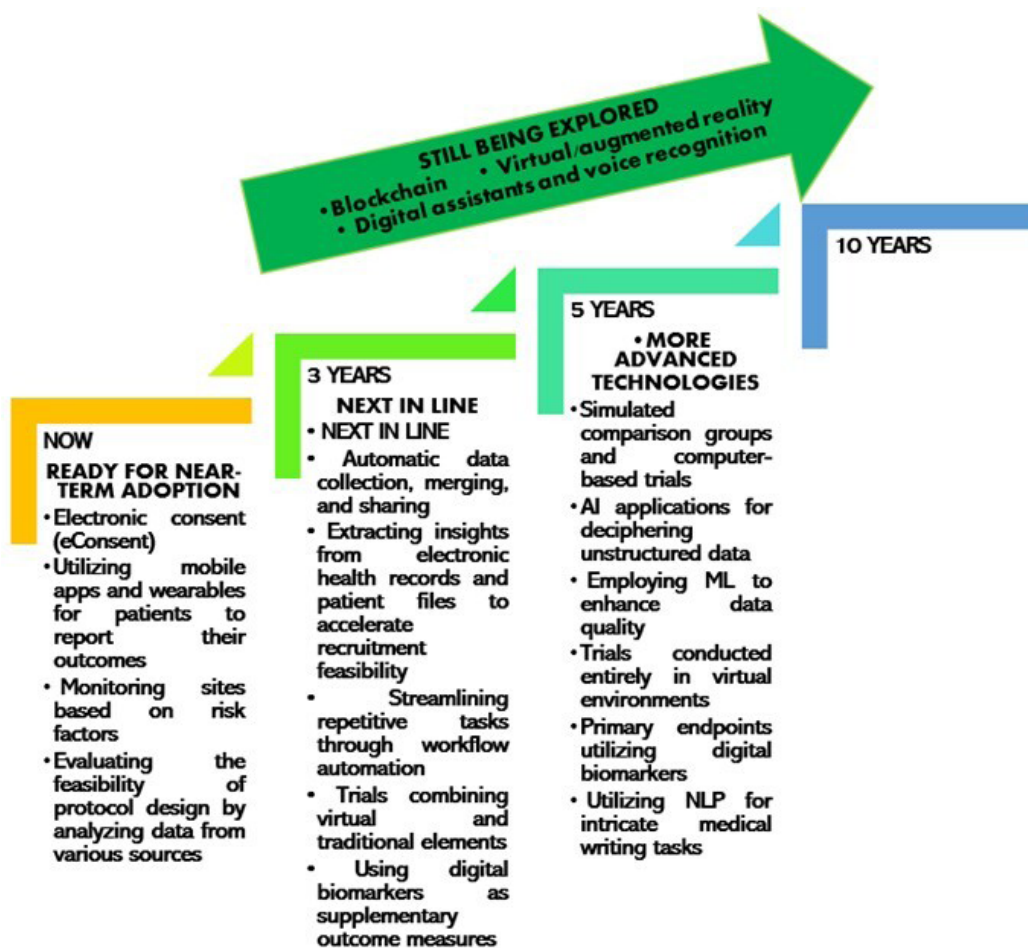
FIGURE 9 - AI Tech Adoption Timeline.

The prospective evolution of regulatory frameworks for clinical trials

Regulators worldwide have issued guidelines to promote the adoption of Real-World Evidence (RWE) strategies by biopharmaceutical companies. The FDA is at the forefront of this effort, offering directives such as the "Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics" guidance for the industry. The 21st Century Cures Act, enacted in 2016, aims to expedite the introduction of innovations to patients more efficiently and swiftly. (Morrrison, 2019). The FDA recognizes the substantial potential of employing digital technologies to bring clinical trials to patients, believing that increased patient engagement and participation from a variety of populations receiving healthcare may be fostered via more accessible trials. As the volume of Real-World Data (RWD) submitted to the FDA grows in diversity, speed, and size, the FDA is increasingly deploying Deep Learning (DL) and Natural Language Processing (NLP) tools in its regulatory procedures. The FDA is launching an intensive fellowship program that allows postdoctoral students from prestigious colleges and universities to join the agency for two-year fellowships focused on developing effective AI-based regulatory science tools, as well as developing FDA educational programs on AI in collaboration with external academic partners, to address the need for AI expertise and the difficulties in finding and keeping qualified talent. Regulatory frameworks for clinical trials are expected to evolve in the future to keep up with technological advancements and improve access to clinical trials. Here are some potential ways regulatory frameworks for clinical trials might evolve:

- Specific regulatory frameworks for virtual studies are expected shortly. (Gordon, Mandl, 2020). This will help improve access to clinical trials and make them more efficient.
- To guarantee that clinical trials in the UK genuinely collaborate with patients and the public and are inclusive of the range of individuals who could benefit from the medication if the data produced eventually results in regulatory approval, extensive new guidelines will be unveiled in tandem with new legislative measures. (Hardman *et al.*, 2023) To evaluate novel, fit-for-purpose methods in clinical investigation, a regulatory framework will be required. (Leyens, Simkins, Horst, 2022). To meet patient and data demands for the particular context of usage, this will assist project teams in choosing appropriate creative techniques for the job.
- An environment that supports the conduct of large multinational clinical trials and creates links between the research and development. (EMA, 2022). This will help improve access to clinical trials and make them more efficient.

Recent changes in regulatory frameworks for clinical trials include:

- The Clinical Trials Regulation significantly altered the EU/EEA's authorization process for clinical trials, allowing sponsors to carry out these studies more effectively. (EUR-Lex, 2022).
- Modernizing clinical trial regulations is a priority for many countries, including Canada. These changes will help improve access to novel therapies while safeguarding patient safety. (Canada.ca, 2022).
- The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK has introduced a series of new measures to streamline clinical trial approvals, facilitating clinical trial administration and approval in the UK more quickly and easily.
- Regulatory frameworks for clinical trial data sharing are becoming increasingly important. A scoping review identified regulatory frameworks and policies that govern clinical trial data sharing and explored key elements. (Mathias *et al.*, 2023).

Changes in research and development are driving regulatory changes in the medical device industry. Regulation is becoming a driver of innovation, and regulatory changes are needed to keep up with the changing landscape of medical device development. (Maresova, 2023).

Forthcoming clinical trials and innovations

The biopharmaceutical industry has been historically hesitant to embrace cutting-edge methods for enlisting and overseeing clinical trials. Nevertheless, with the merging of medical insights, substantial growth in real-world evidence (RWE), and strides in technology and data administration, a revolutionary opening has emerged. The utilization of data through the application of AI holds the capacity to amplify efficiency in clinical trials, enhance patient satisfaction, and expedite regulatory judgments. The life sciences and healthcare sectors are undergoing significant disruption due to interoperable data, secure platforms, and patient-centered care. The integration of AI-driven digital transformation is becoming an essential strategic move, and biopharmaceutical companies must determine their roles within this transformed health ecosystem. Recent developments in AI and machine learning have the potential to create safer, more efficacious drugs and streamline personalized care. (Amin *et al.*, 2021). Wearable devices, machine learning, and Risk-Based Quality Management (RBQM) are among the top five innovations shaping clinical trials in 2023. The synergy of AI, advanced computer simulations, and personalized medicine will result in in-silico studies, which will rely on sophisticated computer modeling and simulations for drug development and regulatory assessments. In silico trials have the potential to remove the necessity for Phase I studies, which test the safety of compounds on healthy individuals. Although complete virtual clinical trials are not currently feasible due to technological limitations and our knowledge of biology, their advancement will provide significant benefits over the present in vivo experiments. The FDA has already envisioned that in future decades, computer models would provide more than half of the data from clinical trials. Biopharmaceutical companies are poised to create customized treatments that address

the root causes of diseases instead of merely alleviating symptoms. Applications enabled by AI will probably become a standard component of the biopharmaceutical operational model within the next five to ten years. Additionally, AI-powered technological innovations in digital health and patient assistance systems are employed throughout the trial process. This includes the utilization of compliance applications, tools for capturing clinical endpoints and data, and remote trial delivery systems are depicted in Figure 10.
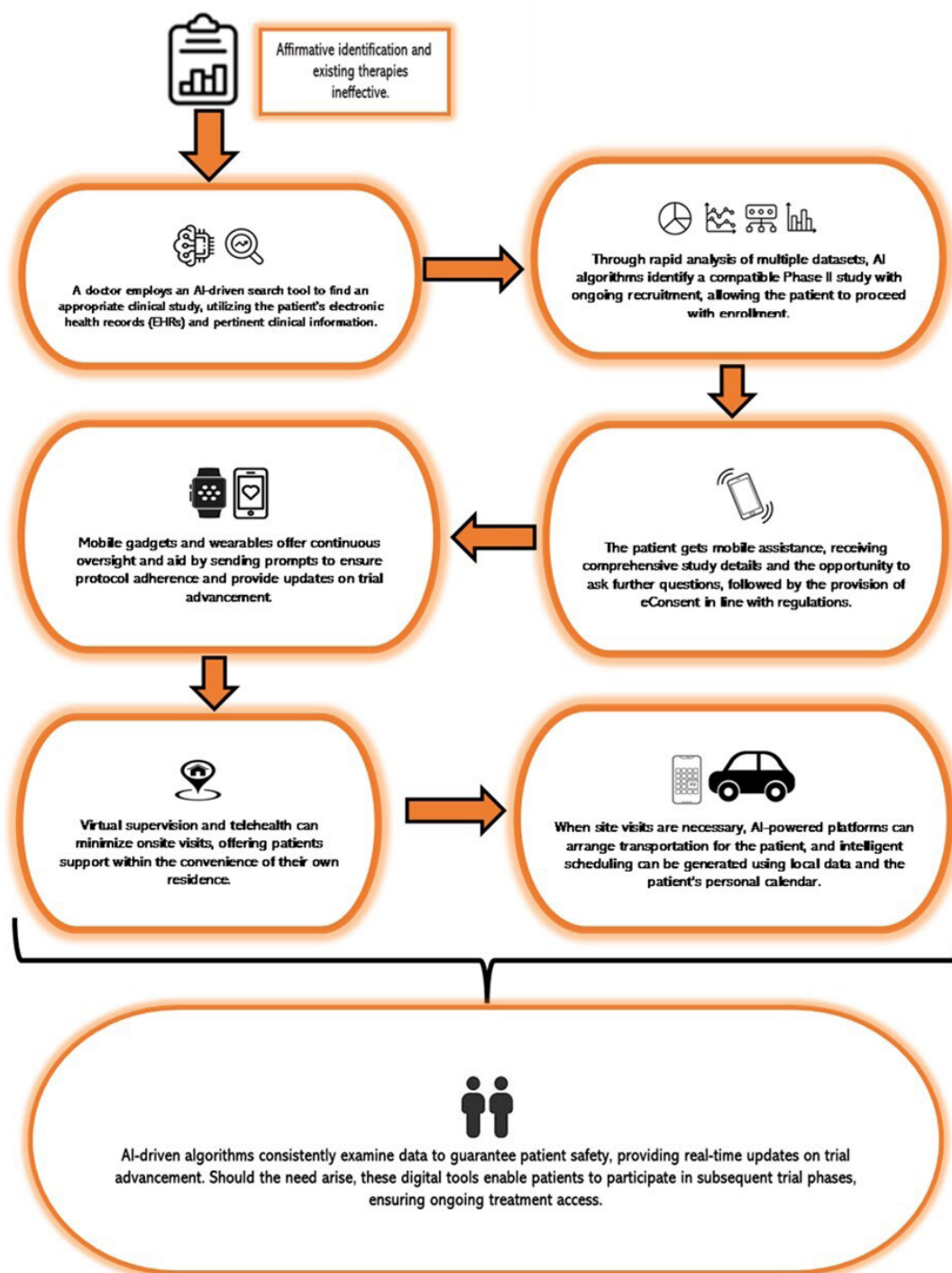
FIGURE 10 - Transforming Clinical Trials with AI-Powered Patient-Centricity.

AI is playing an increasingly important role in clinical trials in 2023. Here are some of the key developments:

- The worldwide market for artificial intelligence (AI) in clinical trials is projected to be valued at $1.4 billion in 2023 and is anticipated to expand at a compound annual growth rate (CAGR) of 16% throughout the forecast period.
- Big pharmaceutical firms are utilizing AI to discover clinical trial participants more quickly or to cut down on the number of subjects required for medication testing, which might speed up drug development and save millions of dollars. (Chopra, 2023) AI integration offers hope in streamlining drug development.

- Phase II patient studies using Insilico Medicine, a biotech business located in Hong Kong and backed by over $400 million, produced the first medication produced entirely by artificial intelligence to enter human clinical trials. (Field, 2023).
- Absci, a generative AI drug discovery firm, created and verified entirely new antibody therapies using zero-shot generative AI, potentially cutting the time needed to bring novel medication options to market in half. (Gangwal, 2024).

Overall, AI is being used to speed up clinical trials, reduce costs, and improve the success rate of drug development. Moreover, before embracing AI solutions, biopharma firms must ponder several crucial questions as in Figure 11.
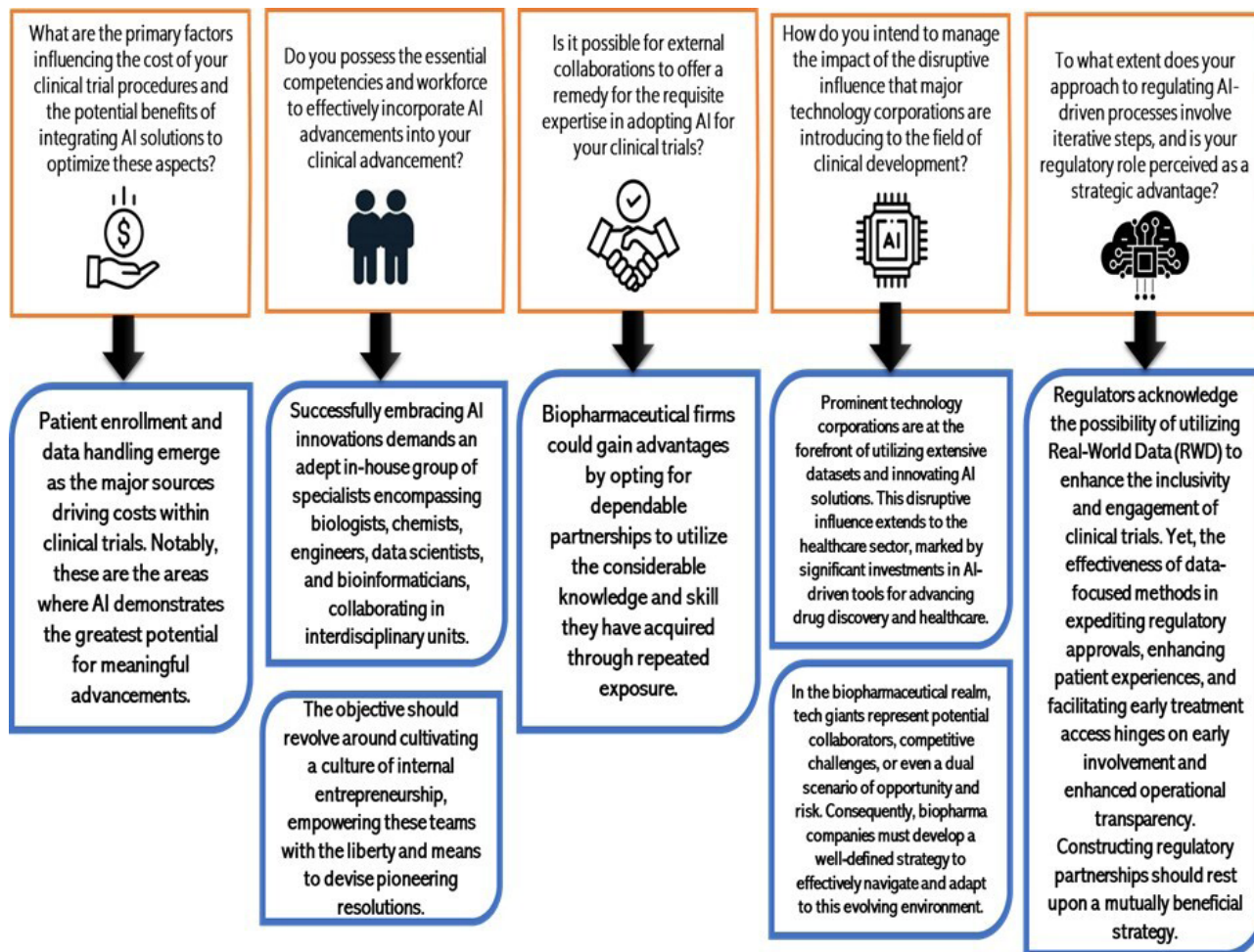

FIGURE 11 - Crucial questions to be addressed before entering into a trial.

CONCLUSION

In the upcoming years, all participants in the clinical trial process will have harmonized their decisions under the desires, necessities, and inclinations of the patients. Sponsors convey information about the trial, its procedures, involved individuals, and processes through the patient's perspective. Sponsors integrate patient viewpoints throughout the design of the study but also establish transparent channels of communication during the execution of the study. This approach has significantly enhanced the efficacy of attracting, involving, and retaining dedicated patients for the duration of the study and even after its conclusion. Noteworthy efforts comprise the adoption of digital therapeutics, which encompass clinically verified interventions, either as standalone solutions or in conjunction with medical products. The biopharmaceutical industry will likely see a paradigm shift in the coming years, with RWE, DCTs, and virtual clinical trials playing increasingly important roles in drug development and indication expansion. The digitization of healthcare and patient medical information will also be a key factor in the industry's evolution. In the times ahead, biopharma enterprises will harness the digital revolution in healthcare to orchestrate clinical trials from a distance.

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