AI in Drug Discovery and Development

Prof. Rajnish Kumar
Dept. of Pharmaceutical Engineering and Technology
IIT-(BHU), Varanasi

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Welcome to the course "AI in Drug Discovery and Development." In today's session, we will have an overview of the clinical trials. So, by the end of this lecture, you will be able to define clinical trials and their role in drug development, outline key historical milestones in clinical trial evolution, and understand ethical principles. Global regulatory frameworks describe the phases and special designs of clinical trials, explain the clinical trial approval and registration process in India, and identify recent innovations and challenges in clinical trial conduct. So, let us see what a clinical trial actually is. So, as we have already seen, drug discovery and development is a highly challenging task, and the first part is preclinical drug discovery, where we try to identify a drug target and validate it.

And then further identify hit molecules, which are then converted into hits to leads, followed by lead optimization and preclinical toxicology studies, which are also called IND enabling studies. So, after all these discovery studies, you know. So, next the compound moves to the clinical trial phases that are called the development phase actually. So, a clinical trial is basically a research study conducted on humans to evaluate safety and efficacy.

Potential side effects of medical interventions such as drugs, vaccines, medical devices, or treatment protocols. So, once we have a molecule that has shown exciting results in, you know, animal studies. So, the next step is to make sure that it is working in humans because the purpose is to develop a drug for humans, right? So, we make sure that it is working in humans and has no severe side effects. So, what is important about clinical trials in drug development is that the most important thing is to ensure the safety and efficacy of those treatments. And then, to obtain the regulatory approval, we need to convince the regulatory agencies that this molecule is going to be beneficial, leading to the therapeutic effect, and is devoid of any side effects or serious adverse effects.

It is also being used for the optimization of doses and administration, such as how much the dose should be and what the optimal route of administration of the drug is, whether it is oral, IV, IM, or dermal. So, all those things we can do with the help of the clinical trials decide with the help of the clinical trials. And then the clinical trials help in the development of new and better treatments as well. And then these are being used or are important for disease prevention and public health improvement. And these are used for

continuous monitoring and post-market surveillance as well.

This is usually called post-market surveillance and is referred to as phase four clinical trial. So, if you look at the development or evolution of clinical trials, you can see how they evolved. So, you know, if we go back to around 500 BCE, there was a king named Nebuchadnezzar. So, he did an experiment. So, he ordered his subjects to eat only meat and wine, and then he had another group that consumed only legumes and water.

So later he found that the group of people who were only consuming, you know, legumes and water were, you know, happier and healthier. So, this is documented as one of the earliest comparative trials where two different groups were made. And then those two different groups were, you know, treated or given different foods, and then those comparisons were made between those two groups. If we talk about the Middle Ages, like 1025 CE. So, there was Avicenna's Canon of Medicine.

So he outlined principles of testing drug efficacy, and this became a precursor to the controlled trials as well. Moving to the 18th century in 1747, James Lind conducted an experiment on scurvy. So, on a ship on a cruise in the Salisbury, he compared six different treatments for scurvy and then realized that citrus fruits proved to be the most effective. This one is widely regarded as the first controlled clinical trial. Okay, going to the 19th century, clinical observation and case series dominated.

And then formal controlled trials were rare at that time, and the focus was mostly on medical case reports without standardized protocols. In the 20th century, in 1946, the streptomycin trial by the MRC UK, Medical Research Council UK, was conducted. It was a landmark randomized controlled trial for tuberculosis treatment, and it also introduced concepts like randomization and control groups. In 1962, the Cower-Harris amendments were made, following the Thalidomide disaster. This we have already discussed in, you know, drug discovery; an overview of drug discovery.

So, where was the thalidomide disaster that led to, you know, birth abnormalities in children whose pregnant mothers were taking, you know, the thalidomide drug for treating morning sickness? So, this law mandated proof of efficacy and safety before drug approval, and that was, you know, a big turning point for regulatory clinical trials. And between 1970 and 1980, the growth of good clinical practice standards, ethical oversight, and institutional review boards all came about during this time. And in the 21st century, the emphasis is on transparency, data sharing, patient-centered trials, and adaptive designs. And there is also a rise in digital health, real-world evidence, and decentralized clinical trials. These are quite popular now.

You can do the trial not only at one center; it can be spread to multiple small centers. So that is called decentralized clinical trials. The use of AI/ML for trial design, patient recruitment, and data analysis is becoming more and more popular nowadays. And that is what we are also looking at in this course. Going through the tools and techniques, AI-based and ML-based tools and techniques, which are helping us expedite drug discovery and development.

So, let's look at the ethical principles in clinical trials. So, there were several regulations. So, the Nuremberg Code was approved in 1947. So, it talks about the detailed human experimentation and it emphasizes on voluntary consent. So, you cannot make anyone participate in a clinical trial by force.

So, that participation should actually come voluntarily, and it should also ensure that whoever is conducting the clinical trial. So, they must prove the necessity of beneficence in research as well. Because if it is not beneficial, if it is not gaining any advantages from doing that research, then it is of no use and should not be done. And then the Belmont Report in 1979 emphasizes respecting persons, as well as beneficence and justice. And the ICMR, which is the body in India, upholds the highest ethical standards and ensures that the participants who are participating in the clinical trial, so their welfare shall be taken care of, and there should be scientific validity in conducting clinical trials as well.

So, talking about good clinical practice. So, it was developed by the International Council for Harmonization. So, that is also short-named as ICH. So, it ensures that clinical trials are conducted in a way that protects the rights, safety, and well-being of the participants. So, it has, you know, several pillars that need to be, you know, taken care of, starting from the designing to conducting.

to monitor, record, analyze, and report on the clinical trial. If we look at the importance of good clinical practices, the first and most important thing is that it protects the rights and well-being of the trial participants. Okay, as I said, if you need to take informed consent from the participant, I mean the person who is participating in a clinical trial. And they have certain rights they can withdraw at any time, and so even before starting a clinical trial, they must be made aware of all their rights and the regulations of the clinical trial. And then another part of GCP is to ensure the reliability of clinical trial data.

So, it ensures that the data provided to the regulatory body after the completion of the trial is not fabricated, is not manipulated, is reliable, and also facilitates regulatory approval. And then also reducing the risk of misconduct, fraud, and unethical research practices because there has been a lot of concern over unethical research practices in clinical trials. So, that must be taken care of, and that is the objective of the GCPs. And then the trial

should be clearly described in a detailed protocol so that all the participants, regulatory bodies, and stakeholders have access to the proper documentation of the trial as well. So, coming to the regulatory authorities, there are multiple regulatory authorities.

And so every country or region has its own. For example, in the US, there is an authority called the FDA, or the Food and Drug Administration. The FDA is responsible for regulating clinical trials, drugs, biologics, and medical devices in the United States. So, it ensures that all medical products are safe. Effective and manufactured according to rigorous quality standards, the FDA also provides guidelines on good clinical practice compliance and oversees the approval process for new treatments, so all treatment or drug approvals need to come from the FDA.

If a drug is to be sold in the US market, it may need to be... Make it available for the patients to use in the US. So, it must have been approved by the FDA.

So, they have their proper guidelines for conducting, designing, and implementing clinical trials. And then you have the EMA, which is the European Medicines Agency in Europe. So, the EMA is a central regulatory authority for medicines in the European Union. It monitors medicinal products through a centralized authorization process. And in 2004, the EMA also implemented a procedure for the accelerated approval of pharmaceutical products.

And then you have the WHO. So, WHO sets international guidelines for clinical trials through its GCP framework, and it collaborates with national regulatory agencies to strengthen global clinical research infrastructure as well. So, if we talk about the clinical trial regulations in India, So, in India, we have an agency called CDSCO, which is the Central Drugs Standard Control Organization. So, it lays down the regulations for the conduct of clinical trials in India. And CDSCO is the national regulatory body for pharmaceuticals, functioning under the Ministry of Health and Family Welfare. So, it is essential that all clinical trials conducted in India be in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines, which is commonly referred to as ICH GCP.

And then it is headed by the Drug Controller General of India (DCGI). So DCGI grants approval for conducting clinical trials, reviewing new drug applications and issuing marketing authorizations. So, the DCGI ensures that trials adhere to the new drugs and clinical trials rule 2019, which streamlines the approval process and enhances participant safety as well. So, the new drugs and clinical trials rule came in 2019. So, it was introduced by the Ministry of Health and Family Welfare.

So the major objectives of this rule were faster drug approval for both Indian and foreign pharmaceuticals. Stronger patient protection with clear compensation rules, encouragement for innovation in Indian pharmaceutical research, as well as regulatory simplifications for academic and bioequivalent studies. So, an ethics committee is a group of individuals responsible for ensuring that research involving human participants is conducted ethically, protecting the rights, safety, and well-being of the participants. So, some of the objectives of the ethics committee are to review and approve biomedical and health research proposals and to ensure compliance with ethical principles including respect for persons, beneficence, and justice. So, there are basically a few types of ethics committees, such as institutional ethics committees and IAC, which operate within research institutions such as hospitals and universities.

There are academic centers, and then there are independent ethics committees that are not affiliated with any institutions; these are often involved in clinical trials for private or commercial sponsors. So, the procedure for ethics committee approval is like this: the first step is that the ethics committee needs to get registered. So before reviewing any study, the ethics committee must be registered with the CDSCO, which is the Central Drug Standards Control Organization, or recognized under ICMR guidelines for biomedical research. And once it is registered, the next step is the submission of the research proposal by the investigator. So, the investigator refers to the researcher or the doctors who wanted to conduct a clinical trial.

So they will submit a proposal to conduct a clinical trial to this ethics committee. And that proposal shall consist of the research proposal, informed consent form, investigator brochure, case report form, risk-benefit analysis, and institutional permission. So, after you submit this research proposal, initial screening by the ethics committee secretary happens. and that checks it for you know completeness of the documents compliance with the format eligibility for full board expedited or exemption review. And once that is done, the full board review meeting happens where the proposal is reviewed by the chairperson of the ethics committee.

And then that also consists of other members, like medical, legal, scientific, and lay members. And once that full board review meeting is done, a decision and communication happen where some of the possible outcomes can be either the proposal is approved. It is conditionally approved where some modifications are required, it is deferred, or it is rejected. And once the decision has been made, the approval letter includes the study reference number, the validity period of the study, any specific conditions imposed on the study, and the list of approved documents. And finally, you get post-approval responsibilities where the periodic progress reports are usually submitted annually.

Or, as required, needs to be submitted by the team conducting the clinical trial, and the SAE, which is known as serious adverse events reporting, within 24 to 48 hours of the treatment. Protocol amendments must be re-approved, and the final report at the study completion needs to be submitted to the ethics committee. So, this is how you know the ethics committee approves a proposal for the initiation of a clinical trial. Once a clinical trial proposal gets accepted, the team needs to register it in the clinical trial registry for India before conducting the trial. The clinical trial registry is a free online public platform for registering all clinical trials conducted in India.

The objective is to promote transparency, public accountability, ethical oversight, and the process of submitting. To register it on the clinical trial registry, you need to create an account on ctri.nic.in and then submit the detailed trial information, such as the study design. The principal investigator details sponsors, interventions, and endpoints, and then uploads the necessary approvals, like ethics committee clearance, informed consent documents, and the trial protocol.

And once it is done, it is reviewed by the CTRI, and then the CTRI assigns a CTRI number to the trial. Okay, so if you look at the overall clinical trial phases starting from phase one to phase four. So, you can see here, for example, this is the preclinical phase. Preclinical means the discovery part, starting from target identification to hit identification, and then to lead. And lead and IND enabling studies happen, and then coming to the clinical trials, you have phase one.

Where usually the size of the participants is very small, like 15 to 50 participants, and the duration is also not very long; it can run for several months only, and the objective is The thing is that a healthy person is participating in this trial, and the idea is to evaluate the safety and gather information about how a drug interacts with the human body. And then in phase two studies, which are done for safety and dosing. So, here fewer than 100 patients usually participate in the trial, and then the objective is to evaluate the safety as well as gather information about how a drug interacts with the body. and to decide the dosing, such as how much of the dose will be needed to achieve the desired therapeutic effect. And then you have the Phase 3 study, which is done for safety and efficacy.

So, in this case, almost 10 times the number of phase 2 participants are involved, and here it may go up to thousands or even tens of thousands of participants in this trial. And then the objective is to confirm the effectiveness and monitor the safety of the truck. And once you get, you know, a positive outcome from the phase 3 trial, then it is approved by the, you know, regulatory bodies like the FDA. or, you know, EMA or other regulatory bodies in the respective countries, and then once it is approved, it is available for the for the treatment of the patients in the clinic, the phase 4 clinical trial, which is known as post-

marketing surveillance, also follows. The objective of this is to gather information about the serious adverse events associated with long-term use, and there have been several instances in which several drugs have been withdrawn from the market.

Because of this phase 4 trial, it is quite important to conduct this study as well. Okay, so looking at the role of pharmacovigilance in post-marketing surveillance. So, the post-marketing surveillance, as I said, is the monitoring of drug performance in clinical practice. and the taking of appropriate action to improve patient safety, wherein pharmacovigilance is involved in the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem. So, the key role of pharmacovigilance includes adverse event detection, signal detection, risk assessment, risk-benefit evaluation, and risk management plans.

Collaboration with healthcare professionals, as well as the reporting of adverse events, is important. OK, so that was about your Phase Four trial. Now let us take a look at some special trial designs where you can have, for example, an adaptive trial design. Adaptive trials allow modifications to the trial procedures based on interim data analysis without compromising the validity and integrity of the study, while increasing trial efficiency and reducing resource waste.

And then you have the basket trial design. A basket trial tests a single drug on multiple diseases that share common molecular or genetic markers. So, these are efficient for, you know, rare mutations. And then they speed up the identification of the responsive subgroups, as well. And then you have the umbrella trial design, where an umbrella trial tests multiple drugs on a single disease, stratified by different genetic characteristics. So, it helps to identify the best treatment for each subgroup.

So if you look at the difference between the placebo control and open-label trials, there are various aspects on which we can compare them. So, in the placebo-controlled trials, it is like double-blind, and due to its, you know, double-blind nature, it reduces the bias. Double-blind means that neither the participants taking the drug nor the placebo know which one they are receiving. nor the clinician who is analyzing the data or giving the drug knows what is actually happening, who is getting what. On the other hand, in the open-label trial, there is no blinding.

In that case, the patient or the participant in the trial knows whether he is taking a placebo or another treatment. So that leads to higher bias. And then, if we talk about the aspect of bias and confounding, in the placebo-controlled trials, it reduces bias and controls for the placebo effects. And then in the open-label trials, it increases the risk of bias due to the lack of blinding. Regarding ethical concerns, there are ethical issues about withholding

treatment in the case of placebo-controlled trials.

However, there is less ethical concern in open-label trials because all the participants receive the treatment. And then you have the, if we talk about the real-world applicability of placebo-controlled trials, these are less applicable to daily practice. However, the open-label trials have better real-world applicability where no placebo is involved. And then the placebo-controlled trials are, you know, really expensive because they require a placebo and blinding as well. However, the open-label trials are less expensive and easier to conduct.

And the placebo-controlled trial has higher power, higher statistical power with a placebo baseline. However, the open-label trials have lower power due to the lack of a placebo comparison. So, then there are, you know, inclusion-exclusion criteria and clinical trials, and we will talk about these later in the patient selection as well, or the participant selection. So, however, the exclusion and inclusion criteria determine whether a person can participate in a clinical trial or not. So, based on some factors, they need to be assessed whether they can participate in the trial or not.

So, if you look at the aspect of concern, the criteria for participants' eligibility are the inclusion criteria, and the exclusion criteria are the criteria for disqualifying the participants. So, the purpose of the inclusion criteria is to ensure that only suitable participants are taking part in the clinical trial. However, the purpose of the exclusion criteria is to protect safety and reduce bias in the clinical trial. So, the inclusion criteria may introduce selection bias if it is highly restrictive because we are not giving everyone an equal chance to take part in that trial.

It can cause bias if exclusions are too broad as well. So, if you know, we are excluding almost everyone. So, that is also not good for selecting the participants in a clinical trial. And then about the ethical concerns, the inclusion criteria limit excess if they are too narrow. And then the exclusion criteria exclude vulnerable groups as well, and that is, you know, unfair in nature, actually. Looking at the impact on generalizability, it may reduce real-world applicability; the inclusion criteria and the exclusion criteria further limit the generalizability.

So, these are, you know, some of the aspects on which we have compared both the inclusion and exclusion criteria. Okay, so once we have received approval for the clinical trial, we are now running the clinical trial. So, the thing is that we have to measure how, you know, the clinical trial is working, so for that, we use endpoints, actually. So, endpoints are specific events that are used to determine whether the intervention being studied is beneficial or not. So, there can be multiple types of endpoints; for example, it can be a

primary endpoint where the main result is measured to assess the effectiveness of a treatment.

We can use a reduction in blood pressure in a hypertension trial if we are conducting a clinical trial to evaluate a drug to treat hypertension. We keep the reduction in blood pressure as a primary endpoint and see whether the drug is able to reduce the blood pressure in the participants. So, those who will be meeting the endpoint will be called responders, and those who will not be meeting the endpoint will be called non-responders. And then we can have secondary endpoints, which are additional effects of the intervention; these are not the main focus, actually.

But they can be something that can also be measured. For example, the change in cholesterol levels or the quality of life when we are conducting a hypertension trial. And then there might be composite endpoints that combine multiple individual outcomes into a single measure. For example, major adverse cardiac events which may include heart attack, stroke and death. And then we can have surrogate endpoints as well which indirectly measure to predict the clinical benefit. For example, blood glucose level as a surrogate for the diabetic complications.

If you look at the some of the challenges like they might be you know there can be patient recruitment challenges in the trial. So, those come can come through the lack of awareness of the ongoing clinical trials. and then can be like mistrust in the research because of past analytical research practices or the logistical barriers like distance to trial sites and time commitment as well and language and cultural barriers. So, these you know challenges they are related to the patient recruitment because whenever we are starting a trial, we have to recruit the participants in that trial and these are the challenges which are being faced in designing those in running those clinical trials. So, some of these challenges we will try to see how we can solve by using artificial intelligence or machine learning in the following sessions.

Then we have another major challenge is the patient retention actually. Because sometimes when you have a kind of a lengthy trial, so you have to retain the patients in that trial or participants in the trial and they become like really difficult sometimes. So, they can be due to the lengthy trials because the patients or the participants they have to be there for you know taking the treatment and for the measurement of all those end points. then this can be due to side effects or adverse events as well or this can be due to like inadequate incentives because most of the times those new participants, they join the trials voluntarily and they do not get any you know monetary benefits as well so if there are not not much incentives so then people, they they try to refrain from participating in the trials and then another challenge is the unclear instruction which can discourage continuous continued

participation. And then competing life priorities for example, people have to work, take care of their families and they might have health issues as well which do not allow them to participate to you know retain in those to stay in the clinical trial for longer duration of time. So, there are some ethical concerns actually and public perception of the clinical trials as well.

So ethics in clinical research are emphasized for several reasons. So not only do ethical strategies ensure the integrity of the research results, they also protect the safety of patients who volunteer to participate in the trials. So, some of the core principles, you know, which must be followed are that ensuring that testing is scrupulous and fully complied with stated clinical protocol. as well as verifying the scientific validity of the results as well as choosing clinical trial participants in a way that is fair and free of prejudice and fully informing all volunteers about what the trial involves and potential risk before they offer their consent. So, if you look at the recent developments in clinical trial industry and most of them are related to the artificial intelligence.

So, advances in technology are addressing major challenges in drug trials. So, the key innovations include the inclusion of AI, where AI is providing a lot of help in patient recruitment, where it helps quickly identify suitable participants by scanning their patient data in real time and thereby drastically reducing the recruitment times. as well as predictive modeling where it can analyze patient data to predict outcomes like treatment effectiveness as seen in studies on antidepressants and cancer treatment and clinical trial design where it can help refine trial protocol by evaluating how different components impact outcomes improving drug discovery and trial efficiency. And then there has been a greater shift to virtual and decentralized trials as well, where the remote patient monitoring is being performed. These trials had to adopt to social distancing measures and lockdowns, especially during the COVID-19 time. Resulting in a shift to decentralized trials, remote patient monitoring became widespread, along with telemedicine, mobile apps and home healthcare services.

And then you have the telemedicine for consultations as well. Virtual consultations replace in-person visits, allowing patients to continue participating in trials without risking exposure to the COVID-19 or other, you know, other communicable diseases. And home delivery of medicines and testing, where the medications, devices and diagnostics were delivered to participants' home to minimize the hospital visits. And these practices have been followed continuously and they have, you know, developed a new, you know, how to say, new way to conduct those trials and those are, you know, virtual and decentralized trials. So, some of the impacts of COVID-19 on clinical trial conduct and regulation. So, the COVID-19 pandemic significantly impacted clinical trial conduct and regulations leading to swift adaptations in trial design, patient monitoring and regulatory flexibility.

So some of the key impacts were the shift to virtual and decentralized trials. So, as I said, it is possible to monitor the patients remotely and doing the telemedicine consultation and home delivery of medications became common due to restriction on in-person visits. And another thing was the regulatory flexibility where regulatory bodies like FDA, AMA, they issued guidance for virtual trials, allowed electronic informed consent and provided emergency use authorization for COVID-19 treatments and vaccines. And the informed consent and documentation changes also happened. So, the adoption of e-consent allowed for remote consent processes, ensuring trials continued without requiring in-person meetings and the real-world evidence and adaptive design where the increased use of real-world data and adaptive trial design enabled quicker response to emerging evidence and the faster development of COVID-19 treatments.

and accelerated vaccine development that we have already seen during COVID-19. So, the COVID-19 vaccine trial used rapid approval process, adaptive design, and global collaboration, setting new precedents for vaccine development, as well as global coordination harmonization where regulatory bodies coordinated globally to ensure consistency and speed in trial approvals, especially for the COVID-19 treatments. Coming to the summary, the clinical trials are the cornerstones of evidence-based medicine, ensuring the safety and efficacy of new treatments, their evolution from ancient experiments to modern regulated trials has been shaped by ethical principles and global standards and the clinical trial process includes clearly defined phases like we discussed phase 1 to 4 and may adopt innovative designs such as adaptive basket and umbrella trials. And in India, the trials must comply with the New Drugs and Clinical Trials Rule 2019, need to obtain ethics committee approval and register with the CTRI. And recent trends like AI integration, decentralized trials and real-world evidence are transforming trial design, monitoring and execution. And the COVID-19 pandemic accelerated regulatory flexibility and innovation, reshaping the future of clinical research globally.

that has shown us a you know completely new way of doing all those things so I have an open question for you here so if digital twins like those virtual replicas of human patients could accurately simulate drug responses could they one day complement or even replace early phase clinical trials revolutionizing how we test and approve new therapies so just ponder over it And I have some suggestions for further reading where you can go through these articles to learn more about this topic. And with that, thank you.