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Review Article

Drug Effectiveness Through Clinical Drug Evaluation -Recent Study

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ABSTRACT

This review provides a comprehensive overview of the crucial aspects of medicine effectiveness through clinical medicine evaluation. It covers the stages from clinical trials to post-marketing surveillance, and the factors that impact the balance between benefits and pitfalls of drugs. It also discusses the part of transnational collaboration and arising technologies in enhancing medicine safety. The review aims to inform healthcare professionals and cases about the current state and unborn directions of medicine development and evaluation

INTRODUCTION

The goal of clinical trials is to measure the efficacy and safety of drugs. Traditionally, efficacy has been quantified. By identifying the changes caused by treatments in the variables related to patients' survival rates or to intermediate variables linked to the symptoms of the disease, Usually, such as in cardiovascular diseases or cancer, medical action has resulted in reduced mortality. i.e., an increase in patients' life expectancy [1, 2]. Nevertheless, in recent decades, measurement of quality of life (QOL) has been incorporated as a new dimension of efficacy, complementary to that of life expectancy [3]. In clinical practice, roughly one-third of patients comply adequately, one-third comply somewhat adequately, and one-third do not comply at all [4, 5]. Poor compliance affects the course of many diseases, even those with fatal Prognosis [6]. The degree to which a participant is taking the experimental treatment as directed determines the quality of data regarding a new medication in a therapeutic study. Inadequate adherence poses a significant risk. Possible bias in the way the findings were interpreted Since patients who refuse to take their medication cannot benefit from it, compliance is also crucial for

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assessing efficacy. Because good compliers, irrespective of the treatment administered, typically respond better to experimental medication than do Noncompliers, compliance is specifically linked to the health outcome [7]. The safety requirement for new drug products was established in the 1938 Federal Food, Drug, and Cosmetic (FD&C) Act. As per a 1962 amendment to the FD&C Act, a drug's efficacy must also be demonstrated by "substantial evidence" derived from "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the involved."[8]. Effectiveness has been defined as clinical benefit to the patient and can be demonstrated through clinical outcomes, including longer survival, improved function, symptomatic improvement, or effects on established surrogate endpoints. These clinical outcomes serve as the endpoints in clinical trials approved by the FDA for evidence of effectiveness. An impact on a surrogate endpoint that is reasonably likely to predict clinical benefit may be the basis for approval of a new drug product; these surrogate endpoints are less established than the surrogate endpoints that are currently used in regular approvals, such as the HIV viral load in human AIDS or blood pressure in cardiovascular illness. Clinical trials must be conducted by the sponsor to verify clinical benefit if a medicine is approved under the accelerated approval mechanism; these trials should be initiated at the time of the accelerated approval and should be pursued by the sponsor with appropriate diligence [9].

	Clinical Trials								
	Preclinical testing		**Phase I**	**Phase II**	**Phase III**		**FDA**		**Phase IV**
Years	3.5		1	2	3		2.5	12 total	**Additional Post marketing testing required by FDA**
Test Population	Laboratory and animal studies	File IND at FDA	20- 80 Healthy volunteer	100-300 patient volunteers	1000-3000 patient volunteers	File NDA at FDA	Review process / Approval		
Purpose	Assess safety and biological activity		determine safety and dosage						
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved		

Table 1: Drug Approval Stages in India

Preclinical Testing –

The first step, a preclinical phase, is to find a promising agent, which involves taking advantage of the advances made in understanding a disease, pharmacology, computer science, and chemistry. Breaking down a disease process into its components can provide clues for targeting drug development. For example, if an enzyme is determined to be a key component of a disease process, a researcher might seek ways to inhibit this enzyme.The next step before attempting a clinical trial in humans is to test the drug on living animals, usually rodents. The FDA requires that certain animal tests Be conducted before humans are exposed to a new molecular entity. Establishing the safety of the suggested drug is the

main goal of early in vivo testing. For example, tests should prove that the compound does not cause chromosomal damage and is not toxic at the doses that would most likely be effective. The IND application that is submitted to the FDA is supported by the findings of these testing. The IND application includes chemical and manufacturing data, animal test results, including pharmacology and safety data, the rationale for testing a new compound in humans, strategies for the protection of human volunteers, and a plan for clinical testing. [10,11] If the FDA is satisfied with the documentation, the stage is set for phase 1 clinical trials.

Phase I Trials-

Phase 1 trials concentrate on a compound's pharmacology and safety [12]. In this phase, a limited number of well-trained volunteers receive tiny dosages of a substance under strict supervision. Volunteers who have the illness may be used in situations where it is severe or life-threatening. A phase 1 trial typically enrolls 20–100 people. These studies usually start with very low doses, which are gradually increased. On average, about two-thirds of phase 1 compounds will be found safe enough to progress to phase 2.

Investigating if the medication candidate works as anticipated based on preclinical investigations is the aim of these exploratory studies. Should the study prove fruitful, next research will evaluate the IND's safety and tolerability in human volunteers. These studies typically involve 20–50 healthy volunteers. Apart from determining the drug's maximum tolerated dose by increasing the treatment dose until dose-limiting toxicity is reached (dose escalation), the drug's most common and serious adverse effects (AEs) as well as pharmacological, pharmacodynamic, and pharmacokinetic properties are evaluated. [13].

Phase II Trials-

Approximately 70% of drug candidates move from Phase I to Phase II, in which the therapeutic efficacy of the IND in patients is assessed. [14]

Phase 2 studies examine the effectiveness of a compound. Studies are predicated on an analysis of the minimum number of volunteers required to offer adequate statistical power to assess efficacy, in order to prevent needlessly subjecting a human volunteer to a possibly dangerous material. Typically, phase 2 studies involve 100 to 300 patients who suffer from the condition the new drug is intended to treat. During phase 2 studies, r esearchers seek to determine the effective dose, the method of delivery (e.g., oral or intravenous), and the dosing interval, as well as to reconfirm product safety. [10,15,12,16] Patients in this stage are monitored carefully and assessed continuously. A substantial number of these drug trials are discontinued during phase 2 studies. Certain medications prove to be unsuccessful, while others have unmanageable side effects or safety issues.

During Phase II, subjects are carefully monitored for AEs to further assess the safety of the drug. Moreover, these trials commonly determine the optimum dose regimen to be used in Phase III. [13,17]

Phase III Trials

About one-third of tested INDs transition into Phase III, having 100–500 patients, with the primary objective of confirming the therapeutic benefit of the IND as well as its safety and efficacy in the intended indication. [13] Moreover, the use of different dosages and study populations, and combinations with other therapeutic agents are investigated to provide information regarding indications and contraindications, as well as dose ranges and AEs. As Phase III studies include a larger cohort and have a longer duration than Phase I and II studies, they can potentially reveal rare and long-term side effects. Based on the outcome, 25% to 30% of INDs progress to the next phase. [17,18]

REGULATORY APPROVALS

FDA REVIEW

FDA reviewers will evaluate clinical data, analyze drug samples, inspect the production facilities, and check the proposed labeling. The Federal Food, Drug, and Cosmetics Act requires that there be "substantial evidence" of drug safety and efficacy (19). The FDA interprets this as needing at least two adequate and well-controlled Phase III trials with convincing evidence of effectiveness [20], although this is not a guarantee of approval. The FDA frequently gathers expert advisory committees to examine the data, and it typically heeds the panel's recommendations. Certain constraints, such as those for post-approval (Phase IV) clinical investigations, distribution limitations, labeling modifications, or other criteria, may be attached to approval. FDA review occurs within 180 days of receipt of a complete application [21]. An accelerated process is available for generic drugs, products that provide "meaningful therapeutic benefit" over existing drugs, those that concern serious or life-threatening conditions, or those that address a previously unmet medical need. If it is determined that the application is incomplete, the review process ends and the manufacturer is given a chance to either correct the errors or withdraw the application. In the event that the NDA is rejected, the applicant receives a comprehensive response letter from the FDA outlining the specific shortcomings and offering suggestions on how to strengthen the application. Unsuccessful applicants may request a hearing. The NDA can be reviewed and approved, at which point the firm can start producing and selling the medication. A summary of the timeline, costs, and overall probability of success for the drug development process can be found in [22, 23].

POST MARKETING SURVEILLANCE

The process of keeping an eye out for adverse drug reactions (ADRs) in marketed drugs after clinical trials is known as post-marketing surveillance, or PMS. [24] Since most drugs may not reach the market without passing phase III clinical trials, [25] PMS studies are considered to be phase IV studies. [26] The safety and efficacy evaluations of any new medicinal product via clinical trials will provide only limited information on rare ADRs. [27] Additionally, learning what is "rare." 1 in 1000) and "extremely uncommon" (1 in 10,000) ADRs often only arise during the post-marketing stage. [26] This is mainly due to the limited variety of conditions, described as the 'five toos: too few, too simple, too narrow, too median-aged, and too brief', referring to the limited sample size and patient selection criteria, as well as the brief duration of clinical trials. This means that depending solely on these research presents a challenge in obtaining all the necessary safety data. [28] PMS gives more realistic results as they occur in a more natural setting and afford evidence to safeguard or enhance the safety of approved drugs. [29] As a result of PMS, almost 20% of new medications obtained a black box warning post-marketing, and 4% were removed from the market due to safety concerns. [29]

PHARMACOVIGILANCE

The under-reporting of adverse drug reactions is the major setback worldwide, which may be attributed to the lack of time and reporting forms. It has been known that world health organization (WHO) has initiated the program to report all adverse reactions possessed by drugs. [30] The further awareness about adverse drug reactions resulted in emergence of the practice and science of pharmacovigilance, which can be defined as the science of detection, assessment, understanding, and the avoidance of any negative consequences or further potential medication-related issues. [31-32] It is widely accepted that a drug has to go through various phases of clinical trials to establish its safety and efficacy before it is marketed commercially. However, the clinical trials offer various limitations, like: strict criteria

of inclusion and exclusion make them suitable for use in a very selective group of patients; Other factors that cause drug reactions, such as genetic factors, environmental factors, and drug-drug interactions, may not have been studied during the clinical trials. Special demographic groups, such as children, pregnant women, and the elderly population, are not studied during the studies. [33] Hence, the need of pharmacovigilance has been demanded, which includes the detection, assessment, and prevention of adverse drug reactions in humans. [34-35] Moreover, its concerns have been widened to include the herbal drug products, traditional and complementary medicines, blood products, biologicals, medical devices, and vaccines. In addition, pharmacovigilance possesses various roles, like the identification, quantification, and documentation of drug-related problems which are responsible for drug-related injuries. [36-37]

Further, national pharmacovigilance programmes have been introduced, which play a prime role in increasing the public awareness about drug safety. [38-39]

NEED OF PHARMACOVIGILANCE:

It is widely accepted that the clinical development of medicines is a complex process which requires a huge amount of time for its completion. A medication is no longer in the safe, controlled scientific setting of clinical trials once it is launched and is available for public consumption. Most medications have only been tried on a small number of carefully chosen people for short-term safety and efficacy at this stage. Hence, the need of pharmacovigilance arises, which includes securing the early detection of new adverse reactions or patients subgroups of exceptional sensitivity and introducing certain measures in order to manage such risks. [40] Moreover, it is essential that new and medically still evolving treatments are monitored for their effectiveness and safety under real-life conditions after being marketed. Furthermore, more information is generally needed about use in specific population groups like children, pregnant women and the elderly, about the efficacy and safety of chronic use in combination with other drugs. [41-42]

OBJECTIVES OF PHARMACOVIGILANCE

Improvement of patient care and safety in relation to the use of medicines with medical and paramedical interventions remains to be an important parameter. Pharmacovigilance's primary goals include demonstrating the effectiveness of medications by tracking any significant side effects and keeping an eye on their adverse impact profile over a long period of time, from the lab to the pharmacy, improving public health and safety in relation to the use of medicines; encouraging the safe, rational, and cost-effective use of drugs; promoting understanding, education, and clinical training in pharmacovigilance; and effective communication to the general public. [43] In addition, providing information to consumers, practitioners, and regulators on the effective use of drugs, along with designing programs and procedures for collecting and analyzing reports from patients and clinicians, concludes the objectives of pharmacovigilance studies. [32,43]

ROLES OF PHARMACOVIGILANCE

Pharmacovigilance has been widely accepted to possess a significant role in early observation of the risk associated with the drug. All the medicines are tested on a concerned small ratio of population before it is approved for post-marketing surveillance. Pharmacovigilance has been known to possess various roles, like identification, quantification, and documentation of drug-related problems; contribution towards reducing the risk of drug-related problems in healthcare systems; and enhancement of knowledge and understanding of factors and mechanisms which are responsible for drug-related injuries. [33] However, in order to fulfill various roles of pharmacovigilance, the

interactions and influence of many stakeholders in society with decision-making powers have been required, which include politicians at national, regional, and local levels; healthcare administrators; drug regulatory authorities; pharmaceutical companies; healthcare professionals like physicians, dentists, pharmacists, and nurses; academic institutions; media representatives; health insurance companies; lawyers; and patient groups. [44]

RISK-BENEFIT ASSESSMENT

In the past decade, over a dozen high-profile brand-name drugs, including rofecoxib, troglitazone, cisapride, and cerivastatin, have been withdrawn from the market [45]. The US Food and Drug Administration (FDA) established a Drug Safety and Risk Management Division, which is charged with evaluating the safety, efficacy, and abuse potential of drugs, as well as risk management and risk communication. In March 2005, the FDA issued risk management guidance for the pharmaceutical industry, which included three separate guidelines: Premarketing Risk Assessment, Development and Use of Risk Minimization Action Plans, and Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment [46–49]. The FDA was granted the ability to mandate that businesses create and execute a risk assessment and mitigation plan for specific prescription medications in 2007 by Title IX of the FDA Amendments Act. In this era of renewed focus on drug safety, the FDA has called for more creative approaches to conceptualizing, measuring, and applying risk-benefit assessment (RBA) techniques to develop and improve a systematic RBA approach throughout the life cycle of a pharmaceutical product [50–53]. In health care settings, appropriate RBA can offer valuable information for preventive intervention that could save lives, minimize litigation, enhance patient safety, improve health outcomes, and save overall health care costs. [52–56]. In Europe, part of the mandate of the Committee for Medicinal Products for Human Use (CHMP) is to assess the risks and benefits of authorized medicines on behalf of the European Medicines Agency (EMEA). The CHMP updated its recommendations in 2007 and included quantitative risk-benefit analysis to the regulatory agenda after releasing a study that looked at the potential benefits of the benefit-risk models and techniques that were already in use.[57, 58]. Several RBA features were noted as being valuable, even though no specific method was advised. These features include the following: 1) identification of all significant benefits and medically significant risks; and 2) weighting of the risks and benefits based on relative importance and the quality of the available evidence. It was also agreed that in order to investigate the further development of customized methodology, a thorough evaluation of the quantitative RBA approaches that were currently accessible and pertinent to the CHMP was necessary. The EMEA recently created the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, which is in the process of developing an algorithm to articulate safety and benefit profiles for pharmaceutical products.

Regulatory bodies look for infrequent harmful incidents using a variety of techniques. These include a review of data from randomized controlled clinical trials, observational epidemiological studies (case-control, cohort, and cross-sectional analyses), drug-use surveys, automated databases linking drugs and disease, spontaneous reporting (passive surveillance, such as the FDA's MedWatch program), and established patient registries [59, 60].

LABELLING AND PATIENT INFORMATION

Any medication's label should at the at least have the following information: the drug's name, its contents expressed in metric units, the active

components' contents, the manufacturer's name, address, and license number, the batch number, and the dates of manufacturing and expiration. [61]. There is a discrepancy between the label and insert on medication packaging. The FDA must approve the insert, which serves as the government's channel of control over communications between the manufacturer and healthcare practitioners. It is an exhaustive document that is not intended for patients; however, it is not illegal to give the package insert to patients. In 2002, the United States Food and Drug Administration (US FDA) enforced revised standardised labeling by introducing improved print and graphics for over 100,000 over-the-counter drug products [62]. According to these new guidelines, the drug facts panel should have the name of the drug, its active ingredient(s), purpose(s), use(s), warning(s), directions, other information, inactive ingredients, and questions [63]. Drugs that fail to follow these labeling requirements will be termed as misbranded, but the US FDA gave 2006 as the deadline for the enforcement of this regulation [63]. Countries such as Australia do not make it mandatory to reveal the inactive ingredients [64]. Over-the-counter medicine safety is frequently overstated. Anyone visiting a pharmacist without a prescription can obtain the medication. The easy availability of such medication highlights the need for informative and consumer-friendly labels to ensure safe and effective use of the medication by the consumer. The World Health Organization (WHO) has reported that 80 percent of the population in developing countries, particularly in India, is dependent on plant-based traditional medicines for basic health needs [65]. Part IX of the Drugs and Cosmetics Rules of 1945 directs all authorities to ensure that manufacturers of ayurvedic, siddha, and unani drugs display the true ingredients (official and botanical names) used in manufacture, together with the quantity of each [61]. It has been argued that this may not benefit people who cannot read. Opinions differ on whether the consumer should be loaded with all the information that is considered mandatory. Excessive warnings could have as negative an effect on safety and public health as inadequate warnings. Giving people too much knowledge could lead to excessive caution, anxiety, and the development of a generalized fear of medications and the risks they entail. Any medicine, even paracetamol, has certain adverse drug reactions and toxicities. [66]

EDUCATION AND COMMUNICATION

The traditional model of adherence (also known as compliance) does not value patients' beliefs, concerns, and preferences about medicines. Originally developed as a novel method of approaching the process of prescription and taking medications, the concordance model is most frequently employed to specify a partnership-based method of prescribing and taking medications. In a concordant consultation, the patient and the health care professional participate as partners to reach an agreement on when, how, and why to use medicines, drawing on the expertise of the health care professional as well as the experiences, beliefs, and wishes of the patient [67] A key element of concordance is that patients perceive the value of sharing their experiences and attitudes and feel comfortable about doing so. There is evidence that the majority of patients believe talking to health care professionals about medicines is important and useful [68] and that they are happy to discuss their concerns when encouraged to do so by a health care professional. [69] Practitioners' communication style may help patients become actively involved in discussions about their medicines. [70] Patient participation in discussions about medicines and greater involvement in decisions were found to lead to greater subsequent understanding of treatment, adherence, more satisfaction about both the visit

and doctor behaviour, and less regret about the treatment decision [71, 72]. Negative outcomes, such as mismatches and misunderstandings between doctors and patients, may occur if patients do not voice their opinions and concerns. These can result in dissatisfaction, as well as the use of unnecessary medicines and non-adherence. [73,74]

INTERNATIONAL COLLABORATION

With each new alliance, companies can reduce incremental costs while maintaining tremendous enterprise-level efficiencies and leveraging their experience and expertise in drug development through global R&D partnerships. The advantages of global R&D partnerships are already being realized by some companies, as indicated by decreasing costs associated with the partnerships, increased flexibility to take on multiple projects or shift resources quickly, and amplified quality and value of product offerings.[75] This model has demonstrated its ability to benefit pharmaceutical companies as well as the public entities that support them. For instance, The Global Fund, an international fund for the acquisition of drugs to treat HIV, malaria, and tuberculosis, ensures a market for future products and offers steady and ongoing support for the research and development of pharmaceuticals and vaccines.[76] In exchange for the intellectual property rights to their goods, pharmaceutical companies that agree to dedicate resources to the research and development of malaria-targeting medications or vaccines might get public money through the Medicines for Malaria Venture, another PPP. [77] The mutual benefit from this kind of international partnership is especially dramatic when considering a global marketplace and the need to cultivate economic growth in developing nation.

EMERGING TECHNOLOGY

In the context of the medical and healthcare industries, the US FDA defines real-world data (RWD) as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources."[78] The rapid generation and availability of digital RWD is a result of widespread use of the internet, social media, wearable technology, mobile devices, claims and billing activities, disease registries, electronic health records (EHRs), product and disease registries, e-health services, and other technology-driven services, as well as increased data storage capacity. [79]. The increasing accessibility of RWD and the fast development of artificial intelligence (AI) and machine learning (ML) techniques, together with the rising costs and recognized limitations of traditional trials, have spurred great interest in the use of RWD to enhance the efficiency of clinical research and discoveries and bridge the evidence gap between clinical research and practice.

CONCLUSION

Clinical medicine evaluation is a vital process that aims to assure the safety and effectiveness of new medicines before they reach the request and beyond. It involves various stages, challenges, and factors that impact the balance between benefits and pitfalls of drugs. It also requires the collaboration of multiple stakeholders, similar as experimenters, controllers, health care professionals, cases, and transnational associations. likewise, it benefits from the advances in technology, similar as real- world substantiation and artificial intelligence, that can give further comprehensive and different data on medicine issues. By understanding and perfecting the styles and generalities of clinical medicine evaluation, the pharmaceutical assiduity can give better treatments and enhance the well- being of cases.

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