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Research Article

EXPANDED ACCESS PROGRAM TO INVESTIGATIONAL DRUGS: A COMPREHENSIVE REVIEW

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A B S T R A C T

When a loved one with a rare condition or serious illness exhausts all treatment alternatives, what do their loved ones go through? It's possible that millions of families are currently experiencing this nightmare throughout the world. US FDA introduced an expanded access program (EAP) in 1987, which provides a compassionate pathway for individuals facing serious or life-threatening medical conditions, especially when standard treatments have been exhausted. There are various categories of EAPs, encompassing single patient Investigational New Drug (IND) Application, Intermediate-Size population IND, Treatment INDs, Emergency Use IND, and Parallel Track EAPs. Expanded access programs have a significant impact on drug development; their contributions to real-world data, improvement of safety profiles, optimization of dosage, and facilitation of prompt patient access to potential medicines are undeniable. A global perspective on EAPs emphasizes their role as beacons of hope in addressing healthcare disparities. The regulatory landscape governing EAPs is explored, focusing on the United States Food and Drug Administration (USFDA), the European Union, and India, with a spotlight on proposed amendments to the New Drugs and Clinical Trials Rules, 2019, in India, suggesting the establishment of a structured regulatory framework in the future. This may provide a pathway to address challenging health situations, offering hope, dignity, and the potential for improved outcomes in the nation.

INTRODUCTION

When a loved one with a rare condition or serious illness exhausts all treatment alternatives, what do their loved ones go through? It's possible that millions of families are currently experiencing this nightmare throughout the world. The last ten years have served as evidence that it only takes one of these cases to spark controversy and possibly lead to reforms in a nation's legal system. Generally, drug or pharmaceutical industries seek USFDA approval for a drug in order to begin a clinical trial, most often enrolling a group of patients. However, not every individual can take part in the clinical trials. Many people around the globe may need such drugs or investigational products as they are exhausted with the old or currently available treatments, or there may be no treatment available for the disorder. In such cases, investigational drugs can be a last hope to cure or improve the quality of life for those patients. The USFDA introduced an expanded access program in 1987, often referred to as compassionate use (CU) programs, standing as a critical and compassionate bridge in the landscape of clinical trials, reaching out to patients facing severe or life-threatening conditions. In the dynamic world of medical research and drug development, where the hunt for innovative therapies is paramount, EAPs carve a distinct path by providing access to investigational treatments outside the conventional clinical trial framework. [(1)]As per World Health Organization (WHO) clinical trials are a type of research that studies new tests and treatments and evaluates their effects on human health outcomes, and act as cornerstone of medical progress, rigorously testing new therapies before they reach the expansive market. [(2)]However, the traditional structure of clinical trials may inadvertently exclude certain patients who urgently need experimental treatments.[(3)]EAPs step in precisely at this juncture, recognizing the pressing needs of individuals who may not meet the stringent criteria of ongoing trials but are suffering from conditions for which no approved therapies exist or have proven ineffective.

While clinical trials follow strict inclusion criteria to ensure data integrity, EAPs broaden the spectrum. They cater to patients who might not fit into the standard trial but could potentially benefit from the experimental treatment. Disease severity, lack of alternatives, and the immediate need for intervention are key considerations in determining eligibility for EAP participation. EAPs provide hope as well as maintain the scientific rigor necessary for drug development. They acknowledge the reality that, for some patients, time is a luxury they cannot afford; thus, by offering access to investigational drugs, EAPs extend a lifeline to those whose situations may be refractory to existing therapies, emphasizing

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the compassionate core of medical research.[4, 5]Compassionate use programs recognize that patients are not merely subjects in a study but individuals facing profound health challenges. EAPs extend beyond the statistical viewpoint of clinical trials, offering a personalized approach that values the immediate well-being of the patient alongside the pursuit of scientific knowledge.The landscape of EAPs is continually evolving as well as shaped by advancements in medical science, ethical considerations, along with regulatory frameworks. As the healthcare community is grappled with the complexities of compassionate access, it is crucial to understand the role EAPs play in advancing patient-centric care and contributing valuable insights to the broader dominion of clinical research.[1, 3]

Types of Expanded Access Programs

Expanded Access Programs are diverse in their structure to accommodate various situations and patient needs. Here are key types of EAPs, each serving specific purposes within the framework of providing access to investigational treatments. Single Patient IND Application also called as Named Patient application is the type of EAP caters to individual patients facing serious or life-threatening conditions. It involves the submission of a Single Patient IND application, allowing a healthcare provider to request access to a specific investigational drug for a particular patient; generally this application is used when the individuals condition is unique, and traditional clinical trial participation is not feasible to patient. [6]Intermediate-Size Population IND is another type of EAP which extends access to a small group of population who share similar medical characteristics. It also allows for a more intermediate-sized population to benefit from investigational therapies. This criteria suitable when there's a collective need among the population with a specific medical condition that warrants access to the experimental treatment.[7]

Treatment INDs are broader in scope and are used when there is a compelling case for providing expanded access to a larger patient population. This type is often employed when there is evidence of the treatment's potential efficacy. This is generally applied when there's a significant patient population that could benefit from the investigational therapy, and when the drug's safety profile supports wider use. [8]Emergency Use IND is typically used when the situations of immediate, life-threatening conditions observed and there is no approved treatments are available only in that cases an Emergency Use IND can be requested. This type of EAP is designed for critical and time-sensitive cases. Furthermore, Parallel Track EAPs run concurrently with late-stage clinical trials which allows patients who do not qualify for the ongoing trial to access the investigational treatment while the drug is nearing regulatory submission. [9]

Impact of Expanded Access Programs on Drug Development

It is important to realize that EAPs do not have a research rationale and data collection is often limited to safety. Although EAPs provide pharmaceutical companies the means to collect additional safety data and expand the safety profile of the therapy, such programs cannot replace clinical trials for investigational purposes. Therefore, compassionate use should not slow down the continuation of clinical trials to provide essential information relative to the benefit/risk balance of a medicinal product. In addition, patients cannot participate in a EAP in case they are eligible for a clinical trial in the envisaged indication of this program.[10]

Participation in EAPs marks a pivotal intersection between addressing urgent patient needs and advancing the landscape of drug development. This program exerts a profound impact, transcending their primary goal of providing access to investigational treatments for individuals facing serious or life-threatening conditions. In the process of real-world data generation, EAP is emerged as an invaluable contributor. By encompassing a diverse patient population, they go beyond the controlled environments of clinical trials, offering a comprehensive understanding of a treatment's safety, efficacy, and potential side effects. This real-world evidence, alongside traditional trial data, shapes a panoramic view that resonates throughout the drug development process.[11]

One of the distinct contributions of EAPs lies in expanding the safety profile of investigational treatments. With a broader patient pool, these programs expose uncommon or rare side effects that might escape notice in smaller trials. This early identification is paramount, navigate drug developers towards refining risk-benefit assessments and ensuring the safety of future patients. Furthermore, EAPs become crucibles for dosing optimization, allowing for the exploration and refinement of dosage strategies based on real-world patient responses. This optimization is not only pivotal for maximizing treatment efficacy but also for minimizing adverse effects, thus refining the therapeutic landscape. Accelerated patient access to promising therapies is a hallmark of EAPs. By providing a pathway for individuals to access treatments before official regulatory approval, these programs not only address urgent medical needs but also afford pharmaceutical companies an opportunity to collect additional data which is advantageous for regulatory submissions.[12]

In the field of drug development, EAPs inform subsequent clinical trial designs. Insights gained from real-world patient experiences refine inclusion criteria, adjust study endpoints, and enhance the efficiency of future studies. EAPs extend beyond clinical metrics, incorporating patient-reported outcomes that delve into the nuances of quality of life and treatment satisfaction. This patient-centric lens enriches the evaluation of treatment effectiveness, aligning drug development with the diverse needs and perspectives of individuals. Furthermore, Expanded Access Programs act as catalysts for early signal detection, exposing both the positive and negative treatment effects. This dual awareness positions drug developers at the forefront of proactive investigation and risk mitigation, ensuring a robust and responsive approach to the evolving landscape of medical innovation.[13]

Patient Outcomes in Expanded Access Programs:

The impact on patient outcomes is substantiable, offering a lifeline to individuals grappling with serious or life-threatening conditions. The alternative provided by EAPs is particularly poignant for those who have exhausted standard treatment options. The outcomes witnessed often transcend statistical measures, manifesting as improved quality of life, disease stabilization, or even remission. For patients navigating the complexities of refractory conditions, EAPs become a gateway to a renewed sense of well-being.The compassionate core of EAPs is reflected in the potential improvement in patients overall quality of life. Beyond the clinical metrics, the programs aim to alleviate symptoms,

enhance functional capacity, and instil a sense of empowerment. Participating in EAPs not only brings forth potential therapeutic benefits but also places patients at the heart of medical research advances. By contributing to the generation of real-world data, patients become active participants in shaping the evidence base for novel treatments. This dual role, as beneficiaries and contributors, underscores the reciprocal relationship between patient experiences and the broader landscape of medical innovation. EAPs foster an environment where hope and empowerment converge. Patients enrolled in these programs find themselves not just recipients of experimental therapies but active participants in their own healthcare journeys. The psychological benefits of hope and empowerment echo in the narratives of resilience and determination that characterize patient experiences within EAPs.[14, 15]

Patient Eligibility Criteria in Expanded Access Programs

The criteria must be met by patient to be eligible to compassionate use of Investigational Drug or Drug product, is described in 21 CFR 312.305(a).Determining patient eligibility is a critical aspect of managing EAPs, ensuring that access to investigational therapies is both ethically sound and aligned with the goals of drug development. The eligibility criteria for EAPs involve various considerations to balance patient needs with safety and scientific rigor. Patients eligible for EAPs need to have a documented and severe or life-threatening medical condition which is considered as a primary consideration, as EAPs are designed to address situations where standard treatments have failed or are unavailable. Patients may need to demonstrate that they have exhausted approved treatment options or that there are no suitable alternative therapies available; because EAPs aim to provide access to investigational treatments when standard therapies have been unsuccessful or are limited, ensuring that patients have explored conventional options first and that person required to show that there are no approved or available treatments that adequately address their medical condition he or she suffering from. This criterion ensures that patients accessing EAPs genuinely there is lack of viable alternatives. [16]

Only those patients who do not meet the inclusion criteria for ongoing clinical trials can be eligible for EAPs as it offers an avenue for patients those do not qualify for participation in traditional clinical trials due to specific medical characteristics or circumstances. Also, there should be a reasonable expectation that the investigational treatment may provide a clinical benefit to the patient and the risks along with potential benefits associated with the investigational treatment is conducted for each patient; which helps to balance the potential benefits with the known and unknown risks is fundamental to ethical decision-making in EAPs. Furthermore, in many cases the treating physician must certify that the patient meets the specified eligibility criteria. Which ensures that the decision to enroll a patient in an EAP is informed by the healthcare provider's expertise and understanding of the patient's medical history. Patients, or their legal representatives, must have the capacity to provide informed consent. Informed consent is a foundational ethical principle, ensuring that patients understand the experimental nature of the treatment, potential risks, and uncertainties. [17, 18]

Global Perspectives on Expanded Access Programs

The fact that EAPs serve as catalyst that provoke precise compassionate use pathways came withrare or untreatable maladies to experimental medicines is one of their distinguishing characteristics on a global basis. EAPs serve as lights of hope in a world where healthcare inequalities endure, providing a means for patients everywhere to obtain potentially life-saving medicines that might not otherwise be available. This worldwide viewpoint emphasises how crucial it is to address urgent medical needs and promote teamwork in order to advance medical knowledge.The regulatory landscape shapes the contours of EAPs in different regions, contributing to a mosaic of approaches and considerations. Understanding international regulatory differences becomes paramount for stakeholders, as they navigate the intricate frameworks governing patient access, safety, and ethical considerations. The harmonization of regulatory standards and the establishment of clear guidelines on a global scale become pivotal steps toward streamlining the implementation of EAPs across diverse healthcare systems.[19, 20]

In the context of patient outcomes, a global perspective encompasses the diversity of healthcare infrastructures, cultural contexts, and disease prevalence. Patients from different parts of the world bring unique experiences and medical histories to EAPs, enriching the pool of real-world data and contributing to a more comprehensive understanding of how investigational treatments perform in varied settings. This diversity of patient experiences becomes a source of strength, driving a global collaborative effort to address urgent medical needs. The Impact of EAPs on drug development resonates globally, influencing the trajectory of research and innovation. Insights gained from diverse patient populations contribute to a richer evidence base, informing not only the development of individual treatments but also shaping the broader landscape of medical science. Collaborative efforts across borders become crucial in harnessing the collective knowledge derived from EAPs, ultimately accelerating the pace of drug development on a global scale. Global perspectives also highlight the importance of ethical considerations in the implementation of EAPs. As these programs strive to balance the imperative of providing compassionate access with rigorous safety and efficacy standards, a nuanced understanding of ethical principles becomes essential. Ensuring that EAPs align with ethical standards recognized internationally fosters trust among stakeholders and contributes to the global acceptance of these programs as integral components of the healthcare ecosystem.[21-23]

Global Regulations for Expanded Access Programs

More and more demands in recent decades have opened the door for pharmaceutical corporations to develop more comprehensive CU programmes and for prestigious regulatory agencies around the world to release guidelines. USFDA launched the expanded or early access programme from the year-1987. Few other legislation have been passed since then. According to the FDA, medications are distributed on a compassionate basis under three primary categories: Increased access for small and medium-sized patient populations; increased access for urgent usage; and increased access for general use. The Food and Drug Administration recently introduced the Form FDA-3926, a document that makes it easier for physicians to apply for medications for those they treat on compassionate grounds. This significantly streamlines

the process. In contrast, the European Union (EU) has implemented the named patient programme and the CU programme. Under the Committee for Medicinal Products for Human usage, the European Medicines Agency (EMA) offers non-binding guidelines. [24]

Regulations in India for Expanded Access Programs (EAPs)

The highest governing body for affairs of drugs as well as medical equipment in the country is the Central Drugs Standard Control Organization (CDSCO). As stated by CDSCO, solely in situations of national emergencies, severe urgency, epidemics, orphan pharmaceuticals for uncommon diseases, and ailments for which there is no treatment, can a novel drug licenced elsewhere than the nation be exempted from clinical trial requirements in the Indian populations. The Drugs and Cosmetic Act 1940 and Rules 1945 (as amended till 31st December 2016) are followed by CDSCO. Despite the fact that the Act does not contain terminology like "Compassionate Use," mechanisms are in place to permit the importation of medications as needed. Medicine manufacturers, healthcare facilities, and individuals can all make requests for the same to the Drug Controller General of India. For the purpose of treating patients with potentially fatal ailments, diseases that result in serious permanent disability, or diseases that require therapies for unmet medical needs, government hospitals or autonomous medical institutions are permitted to import tiny amounts of novel medications under the Rule 33A and 34A of the Drugs and Cosmetic Act, 1940 and Rules, 1945. [24]G.S.R. 354 (E) which is the draft version of certain rules to be amended in the New Drugs and Clinical Trials Rules, 2019 regarding compassionate use of the drug.The draft rules has provisions provided for a) Application for import of unapproved new drug for Compassionate use for treatment of patients by hospitals or and medical institution b) Grant of licence for import of new drug for compassionate use c) Conditions of licence d) Application for the permission to manufacture new drug for Compassionate use e) Grant of the permission to manufacture new drug for Compassionate use, Condition of permission, Inspection of manufacturing site of new drug for the purpose of compassionate use, Suspension or cancellation of permission to manufacture new drug for the purpose of compassionate use. In future this draft rules may be finalized and effective hence achieving the final goal of patient improvement.[25]

CONCLUSION

In the complex field of clinical research as well as drug development, the significance of Expanded Access Programs becomes evident as they serve a fundamental role in addressing untreatable medical conditions and providing a compassionate pathway for individuals facing serious or life-threatening conditions. Patient eligibility criteria in EAPs are multifaceted, and should be considered on the basis of the severity of the medical condition, the patient's treatment history, ethical considerations, and the potential for therapeutic benefit. This careful consideration ensures that expanded access is granted to those who stand to gain the most from investigational treatments while maintaining a commitment to safety and ethical principles.The types of EAPs allows healthcare professionals, regulatory bodies, and pharmaceutical companies to provide access to investigational therapies based on the unique circumstances of individual patients or patient populations. Each type serves a specific purpose in balancing the ethical imperative of compassionate access with the scientific rigor required for drug development. This program plays a vital role in drug development, providing insights into safety, efficacy, and real-world patient experiences. The data generated from EAPs contribute to a more nuanced understanding of investigational treatments, ultimately influencing the trajectory of drug development and enhancing the evidence base for regulatory decisions.While the term "Expanded Access Programs" hasn't been formally declared by CDSCO in India, the Drugs and Cosmetics Act 1940, along with Rules 1945, includes provisions allowing the import of novel drugs as needed. The Central Government has proposed amendments to the New Drugs and Clinical Trials Rules, 2019, suggesting the establishment of a structured regulatory framework in the future. This may provide a pathway to address challenging health situations, offering hope, dignity, and the potential for improved outcomes in the nation.

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