

Expanded Access Programs: Ethical and Practical Considerations for Biopharmaceutical Sponsors

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Abstract

Expanded access is a regulatory mechanism by which an investigational drug can be made available outside of a clinical trial to treat patients with serious or life-threatening conditions for which there are no satisfactory treatment options. An expanded access program (EAP) is the formal plan under which preapproval access to an investigational drug can be provided to a group of patients. Although an EAP is a regulated program, the decision to authorize an EAP is the responsibility of the biopharmaceutical sponsor. Because of the significant impact an EAP can have on current patients, drug development, and future patients, we propose that a sponsor's decision must be based not only on regulatory criteria but also on ethical and practical considerations regarding implementation of an EAP. Such an approach will help ensure that decisions and plans uphold ethical precepts such as fairness, promoting good, and minimizing risk of harm.

Keywords

expanded access, compassionate use, biopharmaceutical, sponsor, ethics

Introduction

The clinical trial process is the primary mechanism by which patients can gain access to investigational drugs before regulatory approval and commercial availability. This process is scientifically necessary to determine the safety and efficacy of investigational drugs and medically and ethically necessary to protect and benefit current and future patients. However, there are occasions when patients with serious or life-threatening diseases or conditions seek access to investigational drugs outside of the clinical trial setting. They and their physician may do so because no approved treatments are available or standard treatments have failed (or are not tolerated), they are unable to participate in a clinical trial, and, because of the severity of their condition, they are unable to wait for commercial availability of a new drug.

To address urgent patient need, many regulatory bodies have sanctioned “expanded access” (often referred to as “compassionate use”) as a mechanism by which an investigational drug can be made available outside of a clinical trial to treat patients with serious diseases who have no satisfactory alternative treatment options.¹ What expanded access entails varies globally. It can include treatment of an individual patient or a large group of patients and may, in some cases,

provide access to a drug between the conclusion of phase III trials and market approval.² Although the term “expanded access” is often used interchangeably with “expanded access program” (EAP), there is a distinction. An EAP is a formal plan under which preapproval access to an investigational drug is provided to a group of patients rather than to fulfill unique individual patient requests. This paper focuses on the EAP category of expanded access; however, the discussion may also be relevant for issues related to individual-patient expanded access (also known as “single patient use,” “named patient use,” or “individual patient investigational new drug application”).

Regulatory bodies operate under the conviction that expanded access is not a requirement but is permissible under appropriate circumstances, as described by specific regulations. Although an EAP resides under the oversight of

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regulators, the decision whether to authorize and subsequently how to implement an EAP is the responsibility of the biopharmaceutical sponsor (hereafter referred to as “sponsor”). Because of the important and sometimes competing interests associated with expanded access and the complexity of running an EAP, authorizing an EAP can be scientifically, operationally, ethically, and emotionally challenging for the people responsible for decision making. Even with the best intentions, it is not possible to satisfy all stakeholders (including patients, physicians, caregivers, regulators, and sponsors). Depending on many variables, it may not be feasible to authorize an EAP or it may not be possible to offer it to all patients in need. With the high stakes involved for current patients, the drug development process, and future patients, it is ethically necessary for a sponsor to proactively identify relevant decision-making considerations.

The purpose of this paper is to stimulate thought and discussion regarding ethical and practical issues relevant to EAP decision making and planning. We propose that a sponsor’s decision to authorize an EAP should be based not only on regulatory criteria but also on implementation considerations: (1) the potential impact an EAP could have on drug development (sometimes referred to as “opportunity costs”), (2) whether an EAP is operationally feasible, and (3) whether it can be conducted in a manner that upholds ethical precepts, such as fairness, promoting good, and minimizing risk of harm. In other words, ethical and practical issues associated with implementation should be additional and necessary considerations for a sponsor’s authorization decision. Considering both regulatory criteria for expanded access as well as implementation considerations will help ensure that authorization decisions are ethically justifiable and that they adequately address the interests of regulators, patients, and sponsors.

Background

On the surface it may seem that EAPs should be authorized because they offer hope for desperate patients. It has been argued that sponsors should provide expanded access to seriously ill patients because it may be their last opportunity for treatment and because these patients are willing to assume the risk of taking an unproven drug. However, EAP authorization decisions are extremely complicated. To appreciate the complexity, it is necessary to understand some fundamental concepts about drug development and associated ethical implications that relate to expanded access.

First, medical knowledge of investigational treatments is fundamentally probabilistic in that it cannot be known with certainty whether a treatment will work, how well it will work, or whether it will be safe. For this reason, investigational drugs must be tested in a well-controlled clinical trial environment

in order to minimize confounding variables and best characterize potential benefit and risk. The clinical trial process is done in a progressive and regulated fashion to methodically build a fund of knowledge. After preclinical testing, small first-in-human studies are conducted (typically, but not always, in healthy volunteers) to evaluate the candidate drug’s safety, including dose, route, and schedule of administration (phase I). Then the drug is studied in a relatively small group of patients with the disease or condition under study to evaluate preliminary efficacy and gather short-term safety information (phase II). Finally, the drug is studied in a larger and more representative population to allow for conclusions about the safety, efficacy, and overall benefit-risk relationship of the drug (phase III). This phase of development also provides the basis for labeling instructions to ensure proper use of the drug. It is only by evaluating data from all 3 phases that a regulatory body can ascertain whether a drug can be considered safe and effective and should be made commercially available.

Even with scientifically reasonable hypotheses and well-controlled studies, however, most investigational drugs do not achieve regulatory approval. Twenty-nine percent of drugs in phase I do not advance to phase II, and 55% of those in phase II do not advance to phase III. Of those investigational drugs that reach phase III, approximately 40% do not obtain regulatory approval.³ The primary reason that investigational products are terminated is because they fail to demonstrate a favorable benefit-risk balance for patients. Important safety issues may not be well characterized until the product is investigated in larger populations in phase III trials or even in post-marketing surveillance. Because of this inherent uncertainty, modern society regulates the drug development process in order to benefit and protect individual patients and the public’s health. Therefore, any access program that deviates from the traditional regulated process of drug development must be scientifically and ethically defensible.

Second, because the benefit-risk profile of an investigational drug is not well characterized (more so in earlier phases of development), there is potential that expanded access use of investigational drug could be ineffective and could seriously harm patients by accelerating the dying process, creating or prolonging suffering, or reducing quality of life.⁴ Because of this possibility, sufficient efficacy and safety data are needed to allow a sponsor to evaluate any potential patient benefits and harms. Therefore, the desire to help patients in dire need of treatment must be balanced with the ethical responsibility to minimize risk and avoid doing harm. As more data are acquired and there is less uncertainty in later drug development phases, then expanded access requests can be evaluated with increasing confidence and decreasing caution.

Finally, within health care, different institutions and different professionals play different roles. A biopharmaceutical

company's primary role is to discover, develop, manufacture, and distribute drugs for the benefit of populations of patients. Ultimately this endeavor benefits both individual patients and society by contributing to the public's health. To create and run an EAP, many resources are diverted from the primary clinical trial effort. Any access program that diverts resources away from a sponsor's primary role and impedes drug development in the short term may threaten the health of future patients by delaying regulatory approval and market access. Therefore, sponsors have an important ethical responsibility to safeguard the integrity of the drug development process, comply with regulatory requirements in the drug review and approval process, and prevent delays in the research and approval of new drugs.

Because of these reasons and because a sponsor has the most comprehensive knowledge about an investigational drug and its own capacity to fulfill requests for expanded access, sponsors are responsible for authorizing an EAP. Yet, beyond regulatory criteria, which provide a framework for EAP decision making, there is little guidance on how to make such a decision. Current published literature on expanded access is primarily centered on legal questions⁵⁻⁹ and policy concerns,^{3,10,11} and authors discuss ethical issues at a conceptual level¹²⁻¹⁴ rather than address ethical considerations for implementation. In the remainder of this article, we highlight regulatory criteria used to authorize an EAP and then offer additional ethical and practical points to consider regarding EAP implementation that may further aid sponsor decision making. The discussion will not focus on what constitutes a "serious disease," nor will it focus on what qualifies as adequate safety and efficacy data or an acceptable benefit-risk balance to justify expanded access.

Regulatory Criteria for Authorization of EAPs

The governing regulatory framework should be the foundation of any discussion regarding EAP decision making. For this paper, we use the US Food and Drug Administration's (FDA) "requirements for all expanded access uses,"¹ which appropriately balance the unmet therapeutic needs of individual patients, the need to protect them from unreasonable risk of harm, and the needs of future patients:

1. The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
2. The potential patient benefit justifies the potential risks of the treatment use, and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
3. Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.¹

In addition to addressing regulatory criteria like these, an EAP authorization decision should include implementation issues, which are often not well recognized. First, a sponsor should consider the impact an EAP could have on broader drug development efforts ("opportunity costs") in addition to criterion 3 above. Second, a sponsor should assess whether it is operationally feasible to conduct an EAP. Operational feasibility will be a key consideration to estimate opportunity costs, but it is also a key consideration for conducting an ethical EAP, as it can be argued that it is not ethically justifiable to initiate a program that is not operationally feasible to maintain. Third, a sponsor should assess whether an EAP can be conducted in a manner that upholds ethical precepts.

Ethical and Practical Considerations for EAP Implementation

The remaining discussion addresses EAP implementation. Ethical and practical considerations are presented together as they often go hand-in-hand and operational realities will determine whether ethical precepts can be adequately addressed.

Impact on Drug Development

A reality of operating any business is that there are limited resources (human, financial, and other), and thus, to be a good steward of these resources, allocation decisions need to support a company's mission and promote sustainability. In the biopharmaceutical industry, a sponsor must responsibly balance the implementation of an EAP with multiple competing obligations. These obligations include not only developing, initiating, and maintaining clinical trials related to the expanded access use of the investigational drug but also undertaking clinical development of the drug for additional indications and developing other investigational drugs in the sponsor's pipeline. In many respects an EAP is competitive with drug development because the resources required to run an EAP, such as scientific, administrative, financial, and drug supply and distribution, are the same resources required to conduct clinical trials and sustain drug development. Because EAPs are not resource-neutral, decisions to authorize an EAP will have de facto drug development consequences to a greater or lesser degree depending on a variety of factors. In some instances an EAP may not pose a significant threat to drug development efforts and thus would be defensible to

authorize. In other instances, an EAP may exhaust limited resources, and it would be ethically defensible to forego an EAP or limit the size and scope of the program.

Operational Feasibility

Size and Scope of the EAP

Before committing to an EAP, a sponsor should take into account the size of the patient population that would be eligible to enroll in the program, the length of treatment (eg, a short-term regimen or chronic administration), and the location(s) where the program could be conducted. Epidemiological data can help a sponsor estimate the potential magnitude and dispersion (eg, disease prevalence and regions) of need and thus also anticipate regulatory requirements for different countries. When conducting this exercise, a sponsor may realize that there are thousands of patients globally who could be identified as potential candidates for treatment, which may not be economically and operationally feasible. In this case, the sponsor may decide either to forego the EAP entirely or put limitations on the program. With the latter option, some patients or locations will necessarily be excluded, and this raises ethical questions about fair access (addressed below).

Clinical Trial Material

Of critical relevance to the decision to authorize an EAP is the availability of clinical trial material (investigational drug). Generally, in early clinical development, only the requisite supply of drug to conduct clinical trials is manufactured. Manufacturing plans are later advanced and expanded as more clinical data support further drug development and planning for potential regulatory approval and commercialization. In the past, as an investigational drug advanced toward regulatory approval, drug supply was less of a concern for an EAP, but this is changing as companies look for new ways to speed drug development. With increased speed, manufacturing demands increase. Thus, in many circumstances, there may not be sufficient manufacturing capacity or material to supply an EAP with drug in addition to supplying ongoing or planned clinical trials, particularly if the EAP is large. If implementing an EAP requires additional drug supply to be manufactured, other clinical studies or other drug manufacturing could become delayed due to limited manufacturing resources. Thus, sponsors are faced with limited options—manufacture more drug supply to run the EAP (at potential great cost), refuse all requests for an EAP and maintain clinical development efforts, or offer an EAP on a limited scale.

In addition to drug supply, regulatory requirements governing labeling, distribution, and importation-exportation of the investigational drug are issues that need to be factored into decision making and planning, regardless of the drug

development phase. Finally, it is important to estimate how long it could take to deliver the investigational drug to a requesting physician once it has been determined a patient meets the EAP inclusion-exclusion criteria. Estimating this time will help the sponsor assess whether it can realistically meet EAP patients' treatment needs and consequently whether an EAP is even practical. The treatment timing demands, of course, will vary with the disease or condition.

Human Resources

In addition to using clinical trial material, an EAP draws heavily upon human and administrative resources to develop, review, approve, implement, and monitor the program. Regardless of scale, an EAP requires the time and effort of research physicians and scientists, project and clinical trial managers, regulatory and safety scientists, materials production associates, supply and logistical managers, and administrative support. Even if each of these specialists spent minimal individual effort, the cost of their collective employ adds up. Perhaps more significant, physicians and scientists with specialized knowledge and expertise are pulled away from other clinical development programs. Outsourcing an EAP to a third party, such as a clinical research organization, may reduce the human resource burden but still requires oversight, financial investment, and drug manufacture, which must be accounted for in the decision-making process. Furthermore, outsourcing the management of an EAP does not relieve the sponsor from its responsibility to ensure proper implementation of the program.

EAP Indications

An early concern when considering an EAP is identifying which indication(s) the investigational drug will be authorized to treat. Depending on a drug's mechanism of action, a sponsor could anticipate expanded access requests for the specific condition(s) already targeted within the drug's current clinical development plan ("on-label indication") or for other conditions ("alternate indications") for which there may be some scientific or clinical rationale or evidence that suggests potential patient benefit. For example, oncology patients often seek access to investigational drugs that may not be under study for their particular cancer type or location. Given the new classes of drugs in development, it is also foreseeable that expanded access could be requested for an alternate indication in a completely different therapeutic area than what is being studied. If a proposed alternate indication use is scientifically legitimate and a drug is deemed reasonably safe for that particular disease state, it may be justifiable to grant expanded access to an investigational drug for the alternate indication. However, a primary concern with treating alternate indications is that the size and scope of an EAP can expand quickly, and subsequently the

resources necessary to implement an EAP will increase with each authorized indication. Furthermore, alternate indication expanded access use may make it difficult or impossible to conduct future clinical trials designed for regulatory approval of that indication due to enrollment challenges.¹⁴ Because there will be a point where an EAP cannot accommodate the volume of related conditions, a sponsor should proactively decide the type and number of indications it can reasonably accommodate and whether the inclusion of other indications could hinder research necessary to gain regulatory approval (and often health coverage) of currently pursued or planned indications.

A related concern is how to deal with alternate indication expanded access requests for children. Typically, investigational drugs are first studied and developed for adult indications in order to establish the safety profile of the new drug and protect children from undue harm. Pediatric expanded access use of an investigational drug being studied in adults can be difficult to justify because the benefit-risk profile either is not known or is not well characterized (depending on phase of development) and because available dosages and/or formulations may not be appropriate for a pediatric population. A sponsor is faced with the challenge of extrapolating from perhaps incomplete adult data the appropriate pediatric dosages and possible pediatric benefit and risk. The sponsor also must assess its ability to provide the drug in pediatric-friendly formulations. In addition to these challenges, there is the concern of how to manage a pediatric EAP should the adult indication not receive regulatory approval. Some of these issues may also be relevant when considering EAPs for rare diseases. In both pediatric populations and rare diseases, these factors should not necessarily preclude an EAP, but there must be appropriate due diligence to ensure adequate protections are in place.

Conducting an Ethical EAP

EAP Limitations and Inclusion-Exclusion Criteria

It is just as important to know when it is appropriate to say “yes” to a patient request for expanded access as it is to know when to say “no,” but excluding any patients from an EAP can be a very difficult decision. Inevitably there are limits to what can be appropriately offered through either clinical trials or EAPs, and limits create boundaries, which are fundamentally discriminatory. Some people will fall inside a boundary and some will fall outside. Yet, “discriminatory” does not equate to “unethical” if there is a rational basis for the constraining criteria. For example, in a clinical trial, inclusion-exclusion criteria are employed to ensure the study will enroll the most appropriate research participants in order to clearly answer the hypothesis. Patients with advanced disease or complex medical conditions are sometimes excluded because they are too ill to respond to treatment or may be at higher risk for potential side

effects. Furthermore, patients with advanced disease could have comorbidities that may confound trial results, thus making the data unreliable. Hence, just as it is not unethical to include or exclude certain patients from a clinical trial, it is not unethical to include or exclude certain patients from an EAP if there is a rational basis for doing so.

The ethical imperative with respect to inclusion-exclusion criteria is that they are objectively defined, scientifically and medically based, and consistently applied. To be ethically sound, the EAP inclusion-exclusion criteria should be justified by a scientific-medical rationale and should not be based on factors that are arbitrary or that entrench inequities (eg, race, social worth, socioeconomic status). Because the purpose of an EAP is to provide treatment (rather than conduct clinical research), a sponsor will need to decide on treatment goals and develop inclusion-exclusion criteria to support the achievement of those goals.

When access to an EAP must be restricted because of the magnitude of unmet medical need or limited drug supply or resources, the inclusion-exclusion criteria can essentially function as a mechanism to allocate a limited resource. The allocation of limited (or scarce) medical interventions has been thoroughly discussed in the literature,¹⁵⁻¹⁷ and sponsors should familiarize themselves with this information. It is important to recognize that there are always underlying values that inform resource allocation decisions, and EAPs are no exception. Generally speaking, the values that inform the allocation of limited medical resources are those that favor the worst off, seek to maximize utility, or aim to treat people equally (discussed in the next section). These values likely will influence treatment goals as well as allocation goals when resources are limited.

Fair Access to an EAP

Appropriate inclusion and exclusion criteria are the primary considerations for an equitable EAP, but there are 3 additional considerations regarding fair access. First, it is possible that access to an EAP may be disproportionately distributed among the well-connected and well-educated classes,^{18,19} and thus only those patients will have a chance to be screened against the inclusion-exclusion criteria. This can be especially challenging when some individuals are capable of generating significant media interest in their story. Any well-intentioned EAP can be criticized as inherently unfair because underprivileged populations may not have equal access to information about an EAP or have routine health care or physicians who can advocate on their behalf to request admission to an EAP. Just as social disparities affect access to traditional health care (globally, regionally, or individually), so too can social disparities affect access to an EAP.

Second, if it can be anticipated there will be a high demand from equally qualified patients, then the sponsor should

consider an allocation plan to manage access—the goals of which are to be consistent and fair across equally qualified patients. Two allocation plans that have been proposed to address fairness are the “first-come, first-served” and “lottery” approaches. The first-come, first-served approach allows those who are first in line during an “open period” to have the first opportunity to access the program, but this may, in fact, favor individuals with power, political influence, or wealth and thus has been criticized because of these types of social disparities.¹⁷ An alternative approach is to conduct a lottery where names are placed in a pool and randomly selected for access.¹⁴ This approach is thought to be more objective as it minimizes favoritism and does not discriminate between equally qualified patients. The assumption is that both of these plans would run until a specified quota of patients is met or a specified time period comes to an end. A challenge with both the first-come, first-served approach and the lottery scheme is that they can ignore relevant differences between patients, such as current health status and prognosis,¹⁶ and thus can still be viewed as inequitable.¹⁴ Thus, it is important to consider how any allocation plan can be used in conjunction with appropriate inclusion-exclusion criteria to promote fair access to the program.

A third consideration for fair access involves the dispersion of EAP locations—whether regional, national, or international. It is a reality of the biopharmaceutical industry that regulatory submissions of new drugs do not occur concurrently in multiple jurisdictions. Additionally, logistical, regulatory, and resource constraints make it impossible to make a drug commercially available in all places where there is a medical need. Similarly, it is impossible to simultaneously initiate EAPs in different regions or implement an EAP in all places with a medical need. Because expanded access regulatory requirements vary by country, the timing or feasibility of an EAP also will differ across countries. Appreciation of global regulations can help a sponsor anticipate locations where an EAP could be opened and managed responsibly as well as anticipate timing for initiating an EAP. The key ethical point for these fair access concerns is that sponsors give forethought to the various allocation and distribution issues and develop plans to equitably manage patient demand.

Closing an EAP

Typically, regulations require an EAP to be terminated when a drug becomes commercially available. At this point the drug is no longer considered investigational for the indication for which it was approved. Thus, it is considered ethical to terminate the EAP and transition patients to traditional health channels or patient assistance programs to obtain the drug. However, this is only applicable for approved indications. If a drug was used for an alternate indication in an EAP (ie, one

that was not or is not under study in clinical trials), then it is uncertain whether and when the drug will be accessible through traditional health channels for that indication. This is a foreseeable ethical challenge. Whether an EAP is for an on-label indication or an alternate indication, sponsors should consider the potential problems that might emerge when ending the EAP and determine how to responsibly transition patients to an appropriate treatment once the investigational drug is commercialized in a given region. Likewise, a sponsor needs to proactively plan how an EAP will be closed if the investigational drug does not receive regulatory approval for the on-label expanded access use.

Conclusions

A clinical trial should remain the primary means to gain access to an investigational drug. However, when expanded access requests can be anticipated, it is incumbent upon a biopharmaceutical sponsor to proactively identify and evaluate the diverse ethical and practical considerations associated with EAP authorization. Knowing when to respond with “yes,” “no,” or a qualified “yes” is an equally weighty responsibility. Even with the best intention to help patients in desperate circumstances, providing investigational drug may not be safe, scientifically or clinically supported, or operationally feasible, or it may not be possible to offer treatment to all qualified patients. Ethical challenges will arise when seeking to balance the immediate needs of current patients with the needs of future patients and when balancing the obligation to protect patients from unreasonable risks with the obligation to do and promote good. Every potential EAP will be different, and the benefit-risk balance to patients and to clinical drug development will vary. Thus, a sponsor’s careful consideration of both regulatory criteria and implementation issues should be requisite to EAP authorization. The ethical and practical issues identified in this paper should not be considered comprehensive, but they should help guide discussion and assist with the very challenging decisions that must be made—knowing there will not be perfect solutions to these challenges, only least-imperfect ones.

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