Access Options for Investigational Products
Key Considerations

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Introduction

Patient access to an investigational product (IP) is available not only through the traditional means of clinical trials but also through various pre-approval access programs. These programs exist under a variety of names including extended access, open label extensions, compassionate use, special access, early access, expanded access, and named-patient programs.[1] Pre-approval access programs come in many forms and the regulations differ from country to country. These programs provide an important service in allowing select patient populations to receive an experimental drug which can thereby benefit both patients and innovators. Pre-approval access programs can be broadly separated into three categories: extended access (XAP), expanded access (EAP) and open label extensions (OLE).

Extended Access Programs (XAP)

Extended access refers to the continued provision of an investigational product to clinical trial participants who were gaining benefit upon completion of the trial. Extended access programs, often referred to as compassionate use programs (CUP), provide a means to bridge the gap between the end of Phase II/III trial participation and country-level product approvals. Extended access programs are sought once a pivotal clinical trial has concluded, yet a large group of trial participants need to remain on the investigational product for therapeutic continuity. These programs also enable the ongoing collection of long-term safety data. The Declaration of Helsinki now recommends that post-trial provisions be made to provide access to participants who still need an intervention that is identified as beneficial during the trial.[2] Extended access programs can be submitted as an amendment to an existing investigational new drug (IND) application/approved protocol or as a separate IND/clinical trial application for this purpose.


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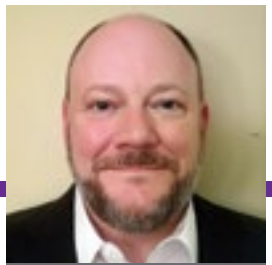
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One method is to design a single, simple master study to allow access for all patients who are receiving benefit from the investigational product. Designing the extended access in this way is advantageous as it can allow the accommodation of patients from multiple parent studies to receive access under one protocol. The extended access program can have minimal data collection requirements, other than safety and the rationales for ending treatment, to ease the burden on trial participants. The new protocol can be implemented quickly by existing sites to coincide with patients completing the parent protocol to provide a seamless continuation of therapy. The programs often follow a more standard of care (SOC) approach to therapy compared with the more intense data collection required within the parent clinical trial(s).

For the innovators, extended access programs can offer an excellent opportunity to collect additional safety monitoring information as well as other targeted endpoints. Although little efficacy data is usually collected under extended access programs, for some rare diseases, these programs can significantly reinforce the efficacy and safety data collection. As with all clinical study programs, the risk of the study must be taken into consideration when designing the program. Concerns often exist around how the ongoing safety data will be managed and viewed by health authorities. This could complicate the evaluation of the safety profile by regulatory bodies during review of the marketing application. One method of addressing this concern is to plan for data analysis early and to ensure linkage of subjects to the parent protocol. Another potential concern for pharmaceutical companies is drug provision. The innovators often delay large scale production until later in the development process, therefore, supply of an investigational drug can potentially be limited. Diverting the supply to extended access programs might limit the availability for the other requisite trials.[3] Other considerations for innovators include what type of reimbursement will be provided to study sites, if permitted per local regulations, and what is the exit strategy to conclude the program at market authorization. The innovators must ensure that clear strategies and plans are in place to address ongoing safety reporting and how analysis will be managed, drug distribution and provision, and an exit strategy from IP to commercial product.

Expanded Access Programs (EAP)

Expanded access programs refer to provision of an investigational product to broader patient populations who have exhausted other treatment options and potentially may gain benefit from the product following completion of standard clinical development, assuming the risk to benefit profiles are favorable. These patients are typically product naïve and did not participate in the clinical trial of the investigational product due to various reasons such as ineligibility, inaccessibility to trial locations, or closed enrollment of the trial. Expanded access programs are often referred to as "compassionate use programs" and can be divided into two primary subtypes: named patient programs (NPPs) and treatment use protocols (cohort programs). NPPs exist under a variety of names in different countries but refer to programs that provide a single provision of an investigational product to an individual patient. Treatment use protocols involve providing a drug to a specified patient population.

Expanded access program requests have been increasing in recent years as demonstrated in Figure 1. Consequently, pharmaceutical companies are facing the need to establish new procedures to handle this increased demand. For example, in 2015 Janssen initiated a pilot program in partnership with the Division of Medical Ethics at NYU Langone Medical Center to develop a standardized review process for compassionate use requests with the goal of ensuring fairness, beneficence, and evidence-based decision-making. This partnership created the Compassionate Use Advisory Committee which consisted of an independent 10-person committee of physicians, bioethicists, and patient advocates to objectively advise on requests for daratumumab. From July to December 2015, Janssen received a total of 160 requests for pre-approval access. An initial screening by Janssen physicians determined that 76 of these requests were appropriate enough to send to the committee for evaluation, of which 62 submissions were selected for pre-approval access. This process enabled Janssen to provide an unbiased decision-making process to ensure the request was appropriate and in the patient's best interest.[4]

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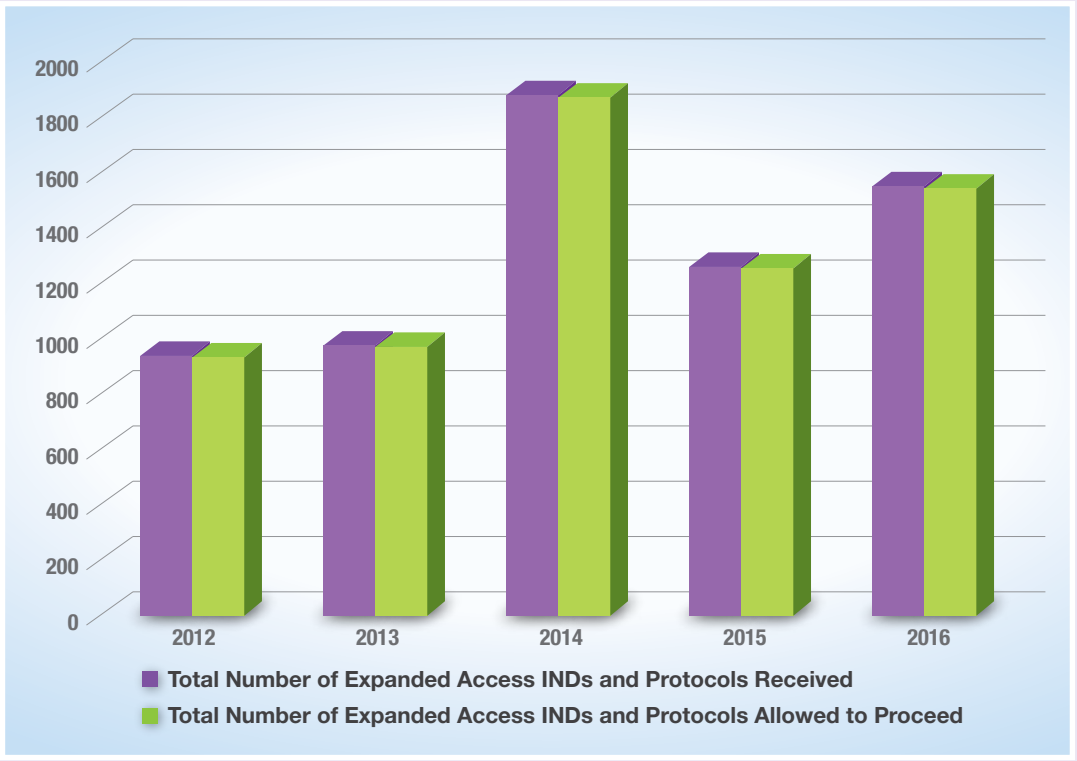
Expanded access programs are intended to provide access to a patient population with a serious disease who have exhausted all commercial options and who meet the general eligibility of the clinical trial population but do not have access to a controlled clinical trial. The design of expanded access or compassionate use programs should involve careful evaluation and planning, including the careful review of available data and a thorough assessment of the risk and benefit profile of the investigational product. Regulatory authorities such as the FDA and the European Medicines Agency (EMA) have specific definitions for these programs. For example, the FDA defines the program to be intended for treating a serious or life-threatening illness for which no other treatment is available, including randomized controlled clinical trials.[5] The EMA provides a very similar definition, allowing EAPs for seriously ill patients who currently cannot be treated satisfactorily

Figure 1. Number of Expanded Access INDs and Protocols Received and Allowed to Proceed by the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA) (2012-2016)[3]

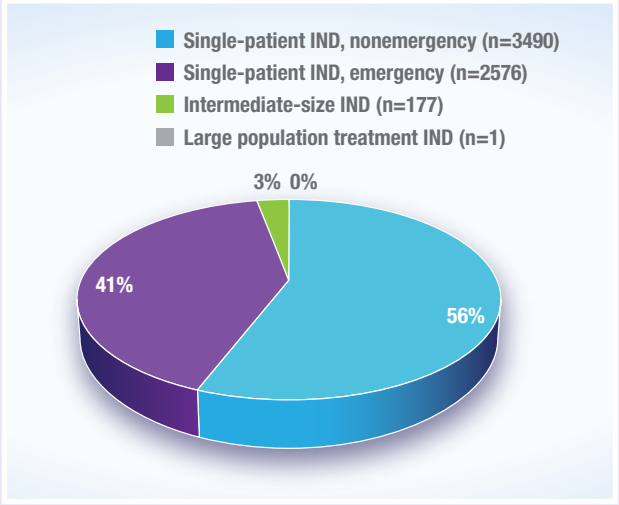


with authorized medicines or who have a disease for which no medicine has yet been authorized. However, in the European Union (EU), expanded access programs are coordinated by the member states which decide how and when the programs are implemented.[6] Additionally, it is worth noting that EU regulation 536/2014, which is scheduled to go into effect in 2019, will change the approval structure of trials and will standardize processes between the member states.

It is also important to determine the type of program to be launched. In the U.S., there are three categories of expanded access programs in place: individual patient expanded access (named patient programs), intermediate-size patient population access, and expanded access for widespread use (treatment use programs). These programs are differentiated by the number of patients participating and the geographic distribution. Figure 2 demonstrates the relative breakdown of these different types of EAP approvals granted by the FDA from 2012-2016. NPPs accounted for the overwhelming majority of these approvals with more non-emergency use than emergency use. For each category, the FDA allows regulatory submission as either a new investigational new drug application (IND) or a protocol amendment to an existing IND.[3]

Additional considerations include global availability, the regulatory landscape, and requirements within the individual country. In the EU, compassionate use programs are coordinated by each member state and they are separate from named patient programs. The level of EMA involvement is, therefore, different for each program.[7] There is often a period of delay between when the sponsor receives the drug's first marketing authorization and the commercial launch of the product. How the expanded access program would be implemented should be factored into its development based on this timing. Other aspects to consider include the types of reimbursement provided (if any) to the site, the responsible party for managing drug shipment and supply, and how safety reporting will be managed. An analysis of 398 expanded access programs from ClinicalTrials.gov determined

Figure 2. Types of IND for Expanded Access Submitted to the CDER of the FDA (2012 - 2016)[3]



that 61% of these programs were industry funded. Most other funding sources came from university or academic sponsors.[8] For investigational products in the late stage of the developmental cycles, having an exit plan in place could provide patients with safer and better transition from the program. This could include implementing a patient assistance program once the investigational product has been approved and commercialized. The timeline for provision of the drug until commercialization is also important to communicate in the guidance.

Open Label Extension (OLE)/Long-Term Extension (LTE)

Open Label Extensions (OLEs) are typically linked to a specific pivotal trial where there is a need to continue subjects on study drug and collect ongoing long-term data points at specific time points to meet health authority needs. The intention is to provide post-trial access for study subjects but with more monitoring rigor related to additional data collection. Figure 3 shows the frequency of published Open-Label Extension studies from 1996-2008.

An OLE is conducted to assess the long-term safety and tolerability of an Investigational New Drug but is also used for continued provision of unlicensed medicines after a randomized trial to patients with medical need of the investigational medicine.

Regulatory Background

From a regulatory perspective, extended access programs are still regarded as interventional trials. Full approval is required by regulatory authorities and ethics committees. The drug must be supplied by the sponsor with investigational product labeling compliant with local requirements (e.g., annex 13 of EU GMP guidelines). A full Clinical Study Report is required at the end of the trial. Promotion of the trial is permitted in accordance with national regulations. Expanded access programs are a rather special case scenario from a regulatory perspective. Patient need must be clearly defined before access is granted. Most compassionate use programs in EU countries are initiated by the innovators; however, named patient programs are entirely initiated by physicians, who bear the liability. Physicians do not typically receive remuneration for their involvement in expanded access programs. Unlike XAPs, promotion of the availability of non-approved medications is not permitted for expanded access programs. Data collection requirements are also generally reduced for EAPs compared to XAPs.

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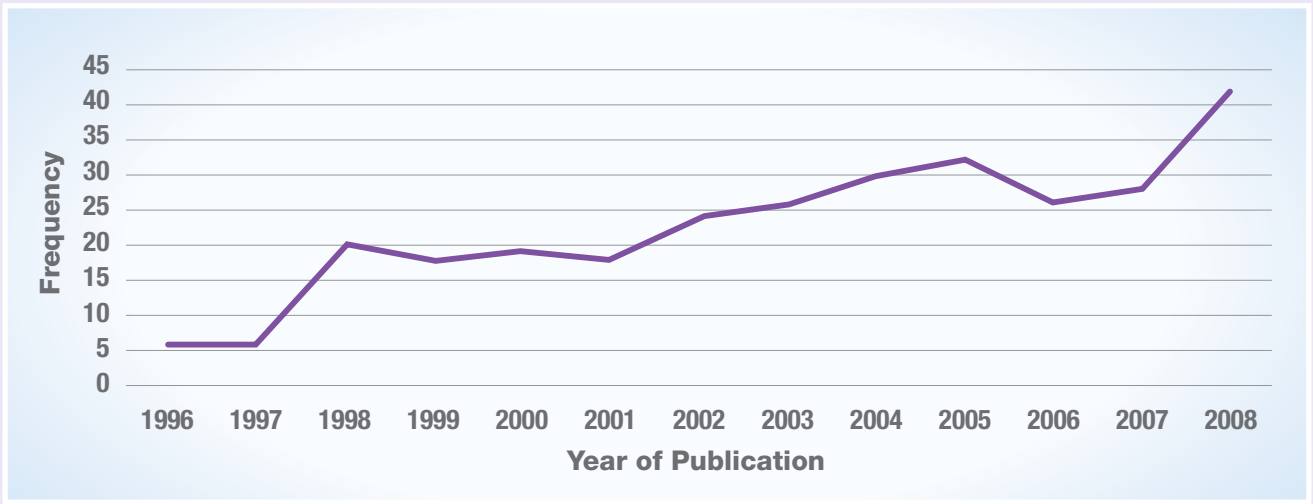
From a global perspective, the regulatory definitions and types of pre-approval access programs vary from country to country. Although the names often differ, these programs can generally be categorized under the three programs, as described above. For example, in Australia, the pre-approval access program is defined by regulatory bodies as the Special Access Scheme (SAS). The SAS program enables access to unapproved therapeutics for a single patient on a case-by-case basis.[10] This corresponds to a named patient program under the definition of expanded access provided in this review. In the United Kingdom, there are two defined pre-approval access programs: Specials Scheme and Early Access to Medicines Scheme (EAMS). The Specials Scheme allows an individual patient to gain access to an investigational drug under the supervision of an authorized healthcare provider (i.e., name patient program [NPP]). The EAMS

Figure 3. Frequencies of Published Open-Label Extension Studies from 1996-2008



(Megan B, 2012[9])

Table 1. Comparison Table of XAPs, EAPs, and OLE/LTE Programs

	XAP	EAP/CUP	OLE/LTE
Aim	**A single, simple study with these characteristics:** • Manages the transfer of subjects from multiple controlled clinical trial programs into one "Platform/Master (XAP)" • Designed to bridge the gap between the end of Phase III clinical trial participation and country level product approvals • Allows continuity of therapeutic benefits	**Initiated to provide access to patients with serious or life threatening diseases and meets these criteria:** • Registration program has concluded • There is clear evidence that the product will benefit a specific patient population • Safety profile well described • There is no other treatment option available, including controlled clinical trials	**Typically linked to a specific pivotal trial and designed to:** • Continue subjects on study drug when needed • Collect ongoing long-term data points at specific time points, to meet health authority needs • Provide a bridge of access for study subjects • Provide more monitoring rigor related to additional data collection when required
Product-naïve patient	No	Yes	No
No other options	Potentially	Yes	No
Data collected	• Safety (and minimal efficacy data) points • Follows SOC while receiving IP	• Safety and Access	• Efficacy and Safety and Post-Trial Access • Assessments and timing of assessments tend to follow Pivotal Program
Pros	• Can close out ongoing clinical program sooner • All patients move to one platform/ master protocol and can be used for entire development program • Typically moves subjects to SOC treatment • Ability to collect limited data sets • Sponsor can control the ongoing patient access more easily • Follows normal regulatory process • Multiple patient access • Streamlined simple protocol • Sites are normally reimbursed for the time spent managing the patient access – more site friendly	**Treatment Use Protocol** • Garner controlled safety data • Multiple site participation • Increases awareness of patient population and product **Named Patient Program** • Less resources • Can start quickly depending on the country • Fits with a low number of requests • No data collection	• Typically for Long-Term Data collection additional data • Single extension per study
Cons	• Follows normal regulatory process – can take longer to set up • Access limited to subjects who participated in Controlled Clinical trial program	**Treatment Use Protocol** • Trial start times more closely mimic typical Phase II/ III trials • Cost consideration versus demand **Named Patient Program** • Does not allow all countries to have access in the same time • Limited monitoring of safety • Spontaneous requests are unpredictable • Difficult to control access from a sponsor perspective • Difficult to control numbers • Physician holds regulatory responsibility and reporting often very time consuming and frustrating for them • Regulatory process can differ for each country, no uniformity • More work for the sites to set up the access • Sites not usually paid – can get frustrated with work	• More data collection requires more rigor and resource to manage • Costly programs • Follows normal regulatory process – can take longer to set up • Access limited to subjects who participated in Controlled Clinical trial program • Single study per controlled clinical trial

enables a broader compassionate use program for patients with life threatening or seriously debilitating conditions.[11] In Japan, there are three programs for pre-approval access: Advanced Medical Care (AMC), Patient-Initiated Mixed-Care (PIMC), and Compassionate Use (CU).[12] These programs cover different patient populations under various circumstances but collectively provide for similar access to those previously described under EAPs and XAPs. Brazil also has multiple options to provide access to unapproved therapeutics. The Humanitarian Use Program allows patients to continue a therapy initiated in a local or foreign clinical trial after it has ended. The Expanded Access Program enables a cohort of patients to receive investigational drug products that are in Phase III trials in Brazil, or in a foreign country if that country has an established expanded access program. An NPP also exists for single patient use.[13] These examples illustrate some of the differences that can occur between countries in their pre-approval access programs. Although the specifics and nomenclature often differ, many countries have similar pre-approval access programs to those defined by the FDA and EMA.

Ethical Considerations with Pre-approval Access

Although the FDA approves more than 99% of the applications submitted for expanded access, the regulatory process can be cumbersome and the pharmaceutical company employees, historically, are the ones providing the case evaluation and assessment.[4] The concern for unknown adverse events and the desperation of running out of options create ethical challenges for the patient, treating physician, sponsor, and society as a whole. Though pre-approval access programs may have the intention of providing patients with increased options, patients may pursue these programs because they are desperate or have unrealistic expectations of the potential benefit. Manufacturers could also be hesitant to provide pre-approval access programs due to the program cost and potential liability for an otherwise promising drug. From a societal perspective, one of the major concerns of widespread pre-approval access is that it may reduce patient willingness to participate in clinical trials. This could compromise the integrity of the drug development goals of establishing safe and efficacious treatment options through evidence-based medicine.[14] Another concern can be that pre-approval programs increase exposure to investigational products that may not ultimately be approved. A recent analysis indicated that 20% of investigational products with expanded-access INDs were approved within one year and only 33% were approved within five years after the initial submission.[15] Although a variety of ethical concerns can arise from pre-approval access programs, they are becoming more common as patients have increasing access to information about potential interventions through the internet and social media. As the industry moves forward with more of these programs, these ethical concerns must be continuously evaluated and addressed. Successful examples have been demonstrated where pre-approval access programs are established through an advisory committee, consisting of members from bioethics, patients, and advocacy groups to achieve a fair and unbiased program for evaluation of the requests.

Summary

Extended access, expanded access, and open label extension programs are important tools to provide different avenues for patients to receive investigational drugs. The need for these programs may increase as regulatory agencies and government bodies place greater emphasis on patient access as demonstrated by the wave of "Right to Try" legislation in the United States, including a bill passed unanimously by the U.S. Senate in 2017. The various pre-approval programs have different advantages and limitations as detailed in Table 1. Many parties are involved in these pre-approval access programs including patients, healthcare providers, pharmaceutical companies, institutional review boards, and regulatory authorities. Ethical and moral considerations from various perspectives compete at times, centering around the balance between patient autonomy and desire for access versus the societal consequences of providing unapproved investigational drugs. Successful real-world examples such as compassionate use or medical review committees have been established by pharmaceutical companies to address these concerns and will likely play an important role as these types of programs increase in public awareness. Real-world evidence can also provide a valuable tool by providing a basis to support use in disease states outside the approved indications. Electronic medical records and other "real-world" sources can help supplement existing clinical safety and efficacy data to provide a rationale for EAP approval. In countries where pharmaceutical companies can charge for EAPs, the price finalized during the EAP process can be used as a benchmark when the investigational product is approved and commercially launched. Moving forward, other considerations such as the influence of social media and internet medicine will also play larger roles in the implementation of these programs. ■

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