Imagine this scenario: A new investigational drug for the treatment of pancreatic cancer is in early phase III clinical trials. Phase II data published show a reasonable safety profile and early indication of effectiveness. There is a buzz in the clinical community, members of patient advocacy groups and a growing number pancreatic cancer blogs buzz with activity.

Every day, the biopharmaceutical company developing the drug receives calls requesting information on enrolling in the trials. They receive requests for direct and immediate access to the drug from patients who cannot participate in trial. The latter group of patients—those requesting access to the drug but who cannot participate in the trial—present a challenge for those in clinical drug development.
In the pancreatic cancer population, where the five-year survival rate with currently available treatment regimens is less than six percent and median length of survival in patients with local disease is ten months, patients do not have time to wait for products to complete development and receive authorization to market. Requests from patients, their families, and their treating clinicians are frequently heavy with sadness, desperation and anguish.

In today’s world, where patients often educate themselves on the Internet and communicate with peers, requests are increasingly accompanied with a well-developed assessment and acceptance of risk of treatment.

For sponsors, the value in providing access to treatment to these individuals is obvious. Yet, there are very real ethical and financial consequences that must be addressed and regulatory requirements that must be met.

By definition, compassionate or expanded access programs (EAPs) are intended to address unmet need and, as such, beyond the regulatory requirements for a given country, no two expanded access programs are alike. The size, duration, geography, operational plan, and cost of program will vary widely depending on the characteristics of the population whose unmet need is to be addressed.

The purpose of this paper is to explore variables to be considered in developing a successful, well-managed EAP that provides access to investigational treatments to patients with terminal or severely debilitating disease and for whom commercially available treatment have failed. The EAP will provide access in a manner that:

• Does not threaten enrollment in or conduct of controlled clinical trials for the drug
• Meets all regulatory requirements
• Does not pose added risk to patient safety and
• Can be financially sustained

EAPs are not set up to support commercial objectives nor are they meant to support analysis or test a hypothesis, though sometimes the data have been very useful in a supplementary fashion.

Making sense of the confusing terminology in compassionate or Expanded Access Programs (EAP)

One of the more challenging aspects of planning an expanded access program is ensuring that all members of the operational team are using the same vocabulary. Vernacular and formal regulatory terms often are used interchangeably, which can be confusing. The definitions follow.

EXPANDED ACCESS is a general term often used to refer to a variety of regulatory mechanisms available to provide investigational treatment access to patients with life threatening or severely debilitating disease for whom commercially available therapies have failed or are not available. For the purposes of this article, the term is used to refer to any such regulatory mechanism worldwide. In the United States, however, the term is used specifically to reference the Code of Federal Regulations Title 21 (CFR 21) Sec 312.300 – 320, which defines the specific requirements for individual patient, intermediate patient population, large patient population treatment protocols, and treatment Investigational New Drug applications (INDs).
INDIVIDUAL PATIENT USE PROTOCOL or EMERGENCY USE PROTOCOL is a request to the U.S. Food and Drug Administration (F.D.A.) to gain access to treatment for one patient who is not eligible for other clinical trial or treatment protocols. There are specific procedures for emergency use in the U.S. under CFR 21 Sec 312.310, which provide for true emergency access requests. Emergency Use Protocol requests must be made prior to the preparation of a written submission that should be distinguished when discussing individual patient requests. The request to U.S. F.D.A. can be submitted by the biopharmaceutical company developing the drug or a licensed physician. When the investigational new drug application (IND) for any type of expanded access program is submitted by a physician, that physician assumes the responsibility of sponsor and is referred to as the Sponsor-Investigator. Another common term used when the physician files the request is Investigator Initiated IND, though this term is not confined to expanded access INDs.

INTERMEDIATE POPULATION TREATMENT PROTOCOL is a request to gain access to treatment for a small patient population in the U.S., generally but not specifically defined as less than 100 patients, who are not eligible for other clinical trial or treatment protocols.

LARGE POPULATION TREATMENT PROTOCOL is request to gain access to treatment for a larger patient population in the U.S., generally but not specifically defined as more than 100 patients, who are not eligible for other clinical trial or treatment protocols. Generally, larger amounts of safety data, and perhaps efficacy data, are required, to support the risk to benefit assessment in a larger patient population. The Treatment Protocol can be filed under an existing IND, or the protocol may be filed with a separate Treatment IND, as is often the case when the population being provided access to treatment is different from the primary indication for the drug. For example, the drug may be in development for the treatment of senile dementia, but the Treatment IND governs expanded access to patients with stroke. These protocols are not primarily intended to assess safety or efficacy [as in a randomized clinical trial], but to treat patients lacking other options.

COMPASSIONATE USE is the general term more commonly used outside of the U.S. to refer to regulatory mechanisms to supply unauthorized product to eligible patients outside the scope of a clinical trial. European Union (EU) legislation allows for the supply of unauthorized product to individual patients. It also allows for cohort programs for certain drugs. The European Medicines Agency (EMA) maintains a published guideline for providing such for compassionate use, but notes that national compassionate use programs either on a named patient or cohort basis are governed by individual Member State legislation.

NAMED PATIENT USE is a specific regulatory mechanism outside of the U.S. to supply controlled, pre-approval access to product at the request of a treating physician for an individual (or “named”) patient who, in the judgment of the clinician, has a special need for it.

COHORT PROGRAM is a specific regulatory mechanism to supply unauthorized product outside of the U.S. to a pre-determined group of patients, outside the scope of a clinical trial, in cooperation with a physician or institution, or with the government depending on the local regulation.

A RANDOMIZED CLINICAL TRIAL is a study in which the participants are assigned in a random manner to separate groups that compare different treatments. This method of assignment is intended to result in the groups of patients in each treatment being similar so that any differences in safety or efficacy data can be evaluated as the result of the treatment. In blinded or masked trials, assignment to a group is not known by participants, investigators or both. This prevents any unintended bias in the evaluations and ensures that data are evaluated objectively. This study design is essential to making the most rigorous conclusions on the safety and effectiveness of a given treatment in the intended population. It is the gold standard of clinical research and is the backbone of regulatory evaluation and market approval.
## EXPANDED ACCESS PROGRAM VS. CLINICAL TRIAL

<table>
<thead>
<tr>
<th>Expanded Access Program</th>
<th>Clinical trial for registration purposes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose:</strong> To provide access to treatment</td>
<td><strong>Purpose:</strong> To evaluate the safety and / or efficacy (or other parameters) of treatment</td>
</tr>
<tr>
<td><strong>Protocol:</strong> Treatment guidelines with treatment plan developed by clinician or treatment protocol</td>
<td>ICH protocol</td>
</tr>
</tbody>
</table>
| **Design:**  
  - Open Label only  
  - Single arm | **Design:**  
  - Blinded or Open Label  
  - Usually Randomized  
  - Cohort only |
| **Regulatory:**  
  - **Ex-US:** NPP or Cohort program | Full investigator contract and study budget |
| Streamlined contract with investigator, usually no payment | Source Documents Verification and more intensive site monitoring |
| Less rigorous site monitoring | **Complex CRFs and Data Cleaning process:**  
  Safety, efficacy, QoL, HE, etc. |
| **Simple CRFs:** Demographic and safety data if data collection permitted by regulation | Full statistical analysis |
| Descriptive statistical analysis, if any | |

**Figure 1.** Similarities and differences between Expanded Access Programs and traditional clinical trials.
Expanding access to investigational treatment can be considered when sufficient data exist to assess the risk to benefit ratio for patients. This can be as early as just after phase II data become available, as noted in the pancreatic cancer example above, or as late as during the review period for the marketing authorization application. Timing is generally driven by the amount of clinical data available in comparison to the need of the patient population.

“Above all else, do no harm” is the credo we live by in medicine. For this reason, the safety profile in EAPs is more important than the efficacy data. Regulators, participating clinicians, and patients require sufficient data to determine that the treatment would not increase or prolong pain or suffering, nor that death would not be accelerated in the absence of any increase in the quality of life.

Sometimes, the requests for expanded access are made early in the development of a drug and the risk to benefit profile must be assessed on lower volumes of data, either from early phase trials on fewer patients, or data from patient populations other than the expanded access request, when patients face immediately life-threatening disease. However, in patient populations for whom death may not be imminent or who face not death but severely debilitating disease, the burden on the amount of data sought to support a risk to benefit assessment might increase accordingly.

The determination to evaluate expanded access does not lend itself to a set of standards or an algorithm, is highly dependent on the patient population’s characteristics, and always requires significant clinical and regulatory judgment. Some sponsors make the determination when the requests for emergency or single-patient use are more than can be handled in the absence of a plan, though this approach is not recommended.

In addition to satisfying patients’ and physicians’ needs by providing treatment options for serious and life-threatening illness prior to marketing, EAPs provide an opportunity to obtain real-world knowledge of the drug, expand the safety database, reveal subpopulations or other indications that should be studied formally, as well as contribute to the relationship between the company and its external stakeholders, regulators, clinicians, and patients.
One of the challenges of EAP programs is to how to scale the program when demand outstrips the original scope.

For an HIV integrase inhibitor for adult patients with limited to no treatment options, PAREXEL worked closely with the sponsor’s global team and local subsidiaries to determine how best to provide access to treatment in 34 countries with an anticipated 1,000 patients enrolled. PAREXEL developed an operational plan that reflected the differences in regulatory mechanisms to provide access to treatment ranging from expanded access provisions to Phase IIIB clinical trial processes.

Demand for access grew from 34 countries to 59 with 950 sites registered at the program’s high point. To meet this demand, PAREXEL deployed a combination of web technologies for clinician registration and a flexible resourcing model that included centralized monitoring able to accommodate treatment demand five times in excess of the sponsor’s original estimates.

In the end, the first patient was enrolled by PAREXEL within 39 days of receipt of the final protocol from the Sponsor and more than 5700 patients were enrolled at 612 sites in 24 countries.
THE WHO

Typically, eligibility for EAPs is limited to patients:

**WITH LIFE-THREATENING OR SEVERELY DEBILITATING DISEASE NOT ELIGIBLE FOR ONGOING CLINICAL TRIALS**

**FOR WHOM THERE IS EITHER NO EFFECTIVE MARKETED TREATMENT**

**WHO HAVE FAILED MARKETED TREATMENT OR NON-DRUG PROCEDURES**

Rigorous study in controlled clinical trials remains the best way for sponsors, clinicians and regulators to provide access to safe and efficacious treatment to patients. As a result, those in drug development must ensure that those trials are enrolled in an appropriate and expedient fashion. Patients eligible for a clinical trial should participate in them if they seek use of the investigational drug.

Expanded access is intended for patients who do not meet the eligibility criteria for those trials. Sometimes, expanded access is used to provide access to treatment in geographies that do not have a center participating in the trial(s) or in a country in which the sponsor will not be able to develop, or register the drug for a considerable period, or circumstances exist where it is not viable to register the product at all. Occasionally, EAPs are also used in orphan drug or rare disease populations, particularly in countries that do not have regulations that help manage the treatment development costs for these diseases commensurately with the very small patient populations.

**CASE STUDY: EXPANDING ACCESS TO PEDIATRIC CYSTIC FIBROSIS PATIENTS**

Enrolling children into clinical trials is always difficult, but when clinicians are unfamiliar with EAP models for pediatric patients, the challenge is multiplied.

For a novel treatment for pediatric patients in cystic fibrosis with limited to now other treatment options, PAREXEL created a scalable operational plan that included the creation of materials and scripts to quickly educate clinicians and onboard staff. In addition, the plan addressed common issues associated with the enrollment of pediatric patients.

Despite a changing regulatory environment, PAREXEL was able to enroll 180 of the anticipated 250 patients at 75 sites within the first nine months of the protocol and deployed the first-in-class EAP in this therapeutic area.
### Major Considerations in Planning an Expanded Access Program

<table>
<thead>
<tr>
<th>Categories</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Managing and Informing Multiple Stakeholders</strong></td>
<td>Sometimes unique internal such as the sales force, and external such as patient advocacy groups (where appropriate)</td>
</tr>
<tr>
<td><strong>Resources</strong></td>
<td>Amount of drug to be supplied, budget, staff required to support and execute program</td>
</tr>
<tr>
<td><strong>Processes</strong></td>
<td>Often SOPs for clinical trials will not support expanded access programs</td>
</tr>
<tr>
<td><strong>Technology</strong></td>
<td>Becomes worthwhile investments as size of program increases</td>
</tr>
<tr>
<td><strong>Drug Distribution</strong></td>
<td>Labelling, importation / exportation requirements</td>
</tr>
<tr>
<td><strong>Access to Local Regulatory Consultants</strong></td>
<td>Ex US landscape can be complicated</td>
</tr>
</tbody>
</table>

A nimble operation approach / plan is required to respond to the unique and variable nature of expanded access programs.

Figure 2. Six major elements to be addressed in a successful operational plan for an expanded access program.
EAPs are subject to local regulations for regulatory, import and/or ethics approval, as well as local ethics committee and hospital procedures and/or policies. Once the local regulations of the country or counties in which expanded access will be provided are known, any unique processes or requirement of local ethics committees or institutional review boards should be identified.

The scope of the EAP must be well defined up front. Some biopharmaceutical companies have established procedures and guidelines for EAPs that can be consulted to help define scope.

Standard operating procedures (SOPs) designed to govern the conduct of randomized clinical trials can burden EAPs with processes not suited for the purpose or leave large process gaps in key areas. With or without specific expanded access policies, the operational plan document for a given program needs to define:

- Country-level regulatory strategies
- Site and patient enrollment process
- Medical review and monitoring
- Data collection
- Safety event reporting
- Drug distribution and controls
- Technology applications and
- Management processes

These are seemingly routine aspects of clinical program planning. Pause for a moment, though, and think about some of these elements within the context of an EAP. The patient population must be defined beyond the primary diagnosis and “unmet need” in most countries. EAPs by definition can support a very broad range of patients, but this is not realistic and can actually be detrimental if the program is loosely structured. Questions to ask when designing an EAP include:

- Are there any restrictions on medical history, concomitant medications, or caregiver support required to prevent a worsening of the patient’s condition upon receipt of treatment?
- Are there considerations that need to be made regarding the impact of the data on the ongoing review of any regulatory applications, potential labeling, or other business requirements?
- How much drug can be provided to support the program?
- Are there caps on the number of clinicians or countries than can be supported?
- How will requests for access for patients who are outside of the scope of the EAP be addressed?
- Typically patients, once enrolled, are supported in the EAP until treatment is commercially available or the request for marketing authorization is declined – how long could this be in the various countries in which the program will operate?
- Are there criteria that should result in suspension of drug shipment?
Thoughtful discussion, leading to sometimes very difficult decisions, on these and similar points will result in a defined scope of patients that can be supported by an effectively managed program.

Often, successful EAPs are executed around “lean” protocols in countries in which the sponsor provides a protocol that fits within the general standard of care. The sponsor seeks the minimum information necessary to manage patient safety and ensure the drug is being used properly by the intended patient.

There have been a noteworthy number of problematic programs executed around a protocol with rigid visit windows, a high number of protocol-specific procedures, extensive data collection, and additional laboratory requirements. These programs incur costs similar to Phase IIIb trials, drain resource from randomized clinical trials, frustrate clinicians and patients with little to nothing to show for the added requirements given the innate limitations of the data set.

Sponsors need to consider the risk of a negative impact on their program from safety signals seen in the EAP. The question needs to be asked if patients are too sick to enroll. If someone is dying and beyond the likely benefit of the drug, and access is provided, the safety data can be confounding.

Companies need to be able to define who should (and should not) be able to gain access to the EAP, thus inclusion criteria for who and how many patients may be treated is important. Factors to be considered in developing budgets include costs of a mixed approach in global EAP programs in some countries and a Phase IIIb clinical trial in others, scalable project and team management, and difficulties in data collection. Sites and patients are not solicited in EAPs as they are recruited into randomized clinical trials.

Once a sponsor makes a program available in a country, it is up to the patients and the clinicians to approach the sponsor with interest. As a result, the numbers of each enrolled in a region or even in general can be wildly different than originally estimated, with significant implications on resource planning, drug distribution and program duration.

**Stakeholders to consider when developing an EAP**

- **External stakeholders**
  - Patients
  - Patient support or advocacy groups
  - Physicians / sites
  - Regulatory authorities
- **Internal stakeholders**
  - Research and development
  - Medical affairs
  - Medical
  - Regulatory
  - Supply chain
  - Legal
  - Clinical operations
  - Commercial / marketing
  - Pharmacovigilance
  - Affiliate or subsidiary staff in countries
CASE STUDY: CENTRALIZED MONITORING ALLOWS EAP PROGRAM EXPANSION

Budget is always a concern that must be balanced with patient access when designing an EAP. When planned and executed correctly, EAPs can be expanded with minimal budget impact.

PAREXEL recently designed an EAP for a single pre-approval treatment for patients with advanced non-small cell lung cancer who had failed standard treatment, could not receive other systemic anticancer therapy, were not suitable for chemotherapy nor eligible for other clinical trials. Among the challenges associated with this program were cross-continental teams operating under a single set of procedures; communication with sponsor affiliates, sites and physicians in more than 70 countries; and, named patient programs in certain countries and clinical study others.

To increase the number of countries for the EAP while keeping patient costs low, PAREXEL used centralized monitoring in two multi-lingual call centers in Paris and Boston.

The program grew many times beyond the original scope to 32,000 patients at 3000 sites in 75 countries. Effective planning and disciplined execution allowed the adaptation of processes and the introduction of new ones to maximize economies of scale and minimize cost increases while maintaining a closely coordinated project. The Sponsor has characterized this study as one of its flagship programs.

We often think then that an EAP can be run with minimal program management compared to a clinical trial. In fact, quite the opposite is true. The cost of an EAP is significant and real, since the program is not delivered according to a fixed plan but instead develops as it unfolds. The operational plan, processes and the management of the EAP must be nimble and dynamic to respond to program changes.

Though EAPs are not on the critical path for product registration, program managers are often surprised by the number of stakeholders whose needs must be addressed with meaningful metrics. The implications to the relationships that the company has with clinicians and patients can be significant.
The reporting of EAP results has to be set up with the end in mind to efficiently close out these programs, manage the transition to commercial supply in a streamlined manner, and satisfy the range of needs. Questions to ask around EAP reporting include:

- How many sites and patients will be enrolled per country compared to the original plan?
- How will additional enrollment affect the drug distribution plan?
- How long will it take on average to provide treatment to patients in a given country?
- Is the time to receipt of treatment appropriately rapid and within the spirit of expanded access? What are the barriers?
- Are sites executing the program in a GCP-compliant manner?
- Of the total CRF pages outstanding, how many represent the minimum required pages for a patient?
- What queries matter and are they getting resolved within acceptable timeframes?
- How will sites be monitored?
- What will be the triggers for an on-site monitoring visit?
- What criteria have to be met a site for the program to be closed there?

With the well-established understanding that resources, both human and financial, need to be prioritized to support randomized clinical trials, it is imperative that the requirements of EAPs be met in ways that minimize costs.

Sponsors need to determine whether they wish to announce the launch of the program (where permitted). If publicly announced, teams need to be ready to manage expectations and respond in a timely manner to contacts following the announcement, press release on the drug, and presentation of data at conferences.

The amount of effort and escalated activities for sites that are slow to respond to requirements following registration must be specified. To assure participants find the program is as worthwhile as it was intended, site feedback from the field or sales staff will need to be heeded.

Sites that have little, if any, clinical research experience may request participation in the EAP. Such sites may not have staff to devote to trial administration and will lack good clinical practice (GCP) experience. The site management approach will need to be structured to address these needs accordingly.

Site staff may need to be able to answer questions from patient advocacy groups questioning whether access to treatment is sufficiently rapid or seeking information of interest to their constituents. Depending on the size of the program and anticipated volume of contacts, a structured communication plan may be beneficial.

In some cases, drug costs or the volume available to support the program may limit the number of patients the program can support. In these instances, biopharmaceutical sponsors must find the most ethical way to manage access. Local features in the clinical or regulatory environment may naturally limit the countries to be considered. Other methods of limiting access include acceptance on a first-come, first-served basis, or enrollment via lottery.

In the U.S., the 2009 revision to the legislation on EAPs clarified that sponsors may charge for direct costs of manufacturing drug and in larger programs, may charge for some indirect costs, such as administrative expenses. However, sponsors have generally found it difficult to quantify the amount to be charged early in the drug’s development.
General clinical supply chain considerations for EAPs include:

- Whether the drug will be shipped to sites in bulk or per patient
- Local labeling requirements
- Expiry date management; returns and destruction policies and procedures
- Storage and distribution requirements (e.g.: 2-8°C or frozen)
- Packaging requirements for cold chain or frozen chain drugs (which cover the full transportation timeline)
- Temperature monitoring and excursion tracking for patient safety
- Import and export requirements
- Distribution tracking and reporting requirements
- How significant changes in the estimated number of requests within a country will be managed to avoid stranding the drug supply while ensuring that medication is available to patients in a timely manner

Drugs are often costly to produce; only available in limited quantities; have short shelf lives and may require cold storage and chilled distribution. The clinical supply chain can become complex and volatile very easily. The focus needs to be on “end-to-end supply chain thinking” to reduce drug wastage and balance supply chain costs; such as production, storage, distribution and comprehensive inventory management. Cost control and invoicing processes need to be established upfront as this can impact tax and financial compliance.

It also must be ensured that track & trace is robust to manage a recall, if required.

Many of the above mentioned items can be achieved by upfront operational planning and supported by enterprise EAP management systems. Ideally a web-based EAP management system should at least fulfill the following set of technical requirements:

- Physicians front end for self-registration, patient enrolment and order generation
- Clinical monitoring front end for site/patient validation, regulatory documents check, status & safety reporting
- Enterprise clinical supplies system for inventory management, warehousing, distribution track & trace, alerting
- Ideally drug safety management such as SAE/SADR reporting and alerting should be embedded.
- A direct interface to EDC data for clinical data collection in context of a clinical trial may be of benefit.

As the program is likely to be ongoing at the time of marketing authorization, a strategy for post-authorization supply will also need to be prepared.
ADDITIONAL CONSIDERATIONS

As previously noted, sites seeking access to treatment may not have research experience nor the staff to support the protocol, which needs to be addressed in a smart manner. Programs cannot support the cost of high numbers of expensive on-site monitoring visits, making structured, effective remote monitoring procedures critical. Monitoring, if performed at all, must be commensurate with the purpose of the program and will need to accommodate features not accepted in controlled clinical trials such as higher percentages of missing data commonly encountered in these programs.

Physicians must first and foremost understand that they generally assume greater responsibility in EAP from the point of request to participate. Clinicians will need to meet their responsibilities with a higher degree of independence since site monitoring will be less intensive.

Historically, investigators were not paid for their time in EAP, though this is changing in some countries. Increasingly, investigators are being paid nominal fees to cover administrative costs associated with regulatory filings and to support the time required to comply with safety data or data reporting in accordance with local regulations. Contracting should be streamlined, though current trends such as site requests for indemnification appear to be on the rise, resulting in a more complex process.

Compared to a randomized clinical trial available data will be limited. In some countries, regulations will prohibit the collection of any data on the patients. For example in Portugal, voluntary data collection is restricted to those spontaneously reported safety data that would be collected for a marketed product. In some countries, such as the U.S., efficacy data can be collected, while in others, such as Australia, it is subject to requirements such as ethics committee approval.

Sponsors should be aware that some countries preclude the use of data from the program in any publication or in support of a marketing application. In any event, safety data are critical with any other information on the treatment population often treated as ancillary.

One word of caution is that the metrics used to track, collect and clean any data must be easily filtered to separate the must-have data from the nice-to-have data. Failure to do so will make it nearly impossible to identify and manage data that must be monitored and obtained cost-effectively.
EAPs serve a critical purpose in the treatment of patients with terminal or severely debilitating disease for whom adequate treatment options do not exist. Successful programs are comprised of processes and tools tailored to meet the local regulatory requirements and address the unique needs of the patient population being treated. Based on the characteristics of the population whose unmet need is to be addressed, the size, duration, geography, operational plan and cost of the EAP must be managed.

Randomized clinical trials remain the gold standard to assess safety and efficacy of a drug and it is essential to the integrity of our drug development system that resources be prioritized to support them. Expanded access methods then must deliver these programs in highly cost contained ways to meet the needs of these patients.
WHEREVER YOUR JOURNEY TAKES YOU, WE’RE CLOSE BY.

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