GLOBAL CLINICAL SUPPLIES GROUP

The Bioethics Associated with Expanded Access/Early Access to Investigational Products Outside of Clinical Trials

The GCSG Expanded Access Resource e-Team was established to provide operational guidance and education about Expanded Access supply. As part of its commitment to provide interactive engagement and share knowledge within the clinical supply community, the e-Team recently held a session on "The Bioethics Associated with Expanded Access/Early Access to Investigational Products Outside of Clinical Trials" during the GCSG 2024 US Conference held in Naples, FL.

This white paper summarizes the panel session led by Gretchen Randlett, Executive Director, Expanded Access and Continued Access Supply Strategy at Eli Lilly and Company, and the responses of three subject matter experts. The questions and responses have been edited for clarity and length.

MODERATOR:

- **Gretchen Randlett**
  Executive Director, Expanded Access and Continued Access Supply Strategy, Eli Lilly and Company

PANELISTS:

- **Karen Frascello,** Senior Director, Medical Affairs, Alnylam Pharmaceuticals, Inc.
- **Andrew McFadyen,** Executive Director, The ISAAC Foundation
- **John Atkins,** Operations Lead, Patient Access Operations, Research and Development, Bristol Myers Squibb

BACKGROUND

The important role of Expanded Access

Expanded Access is defined as the use of an investigational medical product or device outside a clinical trial under the following circumstances:

- No comparable or satisfactory alternative therapy
- The risk to the person from the investigational product is not greater than the probable risk of the disease
- Providing the investigational product will not interfere with the initiation, conduct, or completion of clinical trials

Expanded Access is a mechanism to provide a reactive means for individual patients with serious or life-threatening conditions, who have exhausted all available medical options and do not qualify for clinical trials, access to investigational medicines and devices before they are reviewed and approved by a regulatory authority. It is not a mechanism to proactively increase affiliate sales, promote the product, or seed the market prior to registration.

"Patients are becoming more involved in advocating for their own healthcare," said Gretchen Randlett, Executive Director, Expanded Access and Continued Access Supply Strategy at Eli Lilly and Company. "Clinical trials are also becoming more of a healthcare option on a daily basis, and, as a result, more patients are participating in clinical trials. Unfortunately, not every patient will qualify for a clinical trial, and the majority of those who do not qualify cannot wait to get the drug until the drug is commercially available and on the market. Expanded Access or compassionate use serves as another mechanism for them."

SUMMARY OF KEY TAKEAWAYS

- Expanded Access is nuanced and difficult, requiring flexibility
- Companies need to think ahead and prepare a structured framework to make and act upon Expanded Access decisions, including exit strategies
- Regulatory guidance and logistics can be challenging in some countries; vetting and preparation is critical
- Patient advocacy groups can help incorporate the voice of the patient in early phase development and support education and outreach after a pharma company develops its initial framework
- A global clinical supplies team plays a key role as part of a multidisciplinary group to deliver product and overcome challenges to reach patients
- Honesty and transparency are key when ending Expanded Access
- Emotions are a natural part of the job, with some lows and many highs

PANELIST DISCUSSION

Tell us about the main differences you see between clinical trials and Expanded Access.

"I've been transformed by my experiences over the last three years in dealing with compassionate use requests," said John Atkins, Operations Lead, Patient Access Operations, Research and Development at Bristol Myers Squibb.

"While a clinical trial is very structured and controlled, there's not a similar structure for compassionate use requests. There's such a breadth of understanding and knowledge that you have to assimilate. Every country's regulations are different. Every patient's request is different. There are small nuances to everything that you have to consider when determining whether or not we can provide the treatment to the patient, and more importantly, how to supply the drug to the patient. It's a more unstructured, mix of processes that you must adjust to on the fly almost every day."

How do you get Expanded Access requests and manage them?

"Compassionate use requests can come in so many ways with very circuitous routes," said Karen Frascello, Senior Director, Medical Affairs at Alnylam Pharmaceuticals, Inc.

"A request can be from a parent of a patient that has this disease in a very remote country. It can be from a physician who has an interest, perhaps has read some literature, or understands the product is in development (or potentially available) in the US and Europe, but not in their home country. Advocacy groups play a very large role in directing requests to pharmaceutical and biotech companies. Investigators who are running studies where perhaps the enrollment is closed, or they run across a patient who does not qualify for the study. Requests may come in from very high-profile people, such as celebrities or senators, or even an employee or an executive within a company. It's always quite challenging."

"Following the 21st Century Cures Act, my company's website directs everyone to an email for their requests, which is our aim. It's very useful to direct requests to a portal so we can understand, catalog, and collate these in one place."

As a patient advocate, how would you consult or encourage someone to knock on the door of a pharmaceutical company for compassionate use?

Historically, we would go directly to CEOs, no matter how big or how small, to make sure that the voice of the patient was being heard," said Andrew McFadyen, Executive Director at The ISAAC Foundation. "At that time, there was no structured framework in place, no guiding principles or values that companies were using to make these requests."

"It's been an evolution for me over time, and I found a good collaborative space to work within that meets the best interests of patients in need. I work with companies to put together frameworks, guiding principles, and decision-making trees to make fair, transparent, and equitable decisions for all patients who are in need. "

"It becomes difficult when people, such as high-profile people or someone's best friend or relative, don't go through those mechanisms. That approach is very dangerous and very inequitable, and

it could have significant ramifications on the current patient population and even a larger future patient population that could benefit from the treatment."

As a clinical supplies professional, do you have a seat at the table on how decisions for Expanded Access programs are made?

"There is a seat at the table for clinical supplies professionals at BMS," said John. "Usually in late Phase II or early Phase III, we gather a multidisciplinary, multifunctional group of professionals from the clinical development team and global clinical supplies team. We develop a strategy around the Expanded Access and assign roles. With this strategy, we'll know right away whether a request is approved. If approved, we'll go directly to a clinical supply manager assigned to that product, and we begin the process of determining how to get the drug shipped to the patient."

AUDIENCE QUESTION

How do you go about forecasting for Expanded Access to ensure you have supply for your patients?

"We try to establish a strategy early on," said John. "We go individually to all of our countries and ask about a need in their country for the treatment to estimate the number of patients that may opt in. The clinical supply chain is a critical part of that strategy plan development."

Gretchen added her own company's experience. "Sometimes we've been caught off guard," she said. "We didn't know a drug would lend itself to Expanded Access because it's still in early development. And then we get a call in the middle of the night, and we've had to catch up and build the strategy and operational documents."

Should patient advocacy groups be a part of planning an Expanded Access program?

"I take a controversial stance on this," said Andrew. "I believe patient advocacy groups should be at the table at a later stage in the program, not at the inception of the program."

"My son Isaac has been battling a rare disease since he was born, so I understand how a tired parent is working to ensure a rescue is available for their child. During that early phase, every decision or guidance was solely focused on making sure that rescue would be available for our son. Oftentimes, that pathway may not be what's best for the larger patient population. You're looking at a very micro level, but we need to be looking at a macro level and protecting that future patient population."

"I think that at an early stage, engaging with patient advocacy groups or patient advocates is probably the best way to get guidance and include patient voices. Then, down the road, companies can share their early decisions and the pathway that they believe is the best for all patients who are in need of rescue. They can then ask patient advocacy groups, 'How can you help us work from here to implement, educate, and move forward together so that we're looking after everybody that's in need?'"

What are the key considerations you need to think about as you're creating an Expanded Access program?

"Looking at assets early is an absolute best practice. Most companies will not begin these programs until there's sufficient safety and efficacy to make these products available outside of a controlled clinical trial," said Karen.

"It takes a village to make Expanded Access happen. Many expertise areas have to come together, and everybody has a seat at the table: legal compliance, clinical, medical, regulatory, supply chain, and quality, etc. We determine the type of patient that can get access, when we will implement this program, where we can serve patients, and the type of sites and experience level of investigators, among many other factors. It is a multifaceted approach to ensure the success of a program."
"Regulatory knowledge is one of the biggest areas of focus. Every country writes its own regulations, and they vary significantly. The US, for example, looks and feels like a clinical trial 'light.' In Europe, there's a lot of variation in regulation while some Middle Eastern and Asian countries lack any regulation. I think understanding regulations is where most of the 'heavy lifting' occurs. You don't want any significant delays in terms of products sitting in customs for weeks. You have to be prepared so that you can move quickly when a request comes in from a country you've approved to be a part of your access program. From the supply chain side, the product must be ready and have ample supply effectively labeled correctly."

Can you talk about exit strategies? Are they based on commercial availability and reimbursement?

"You can't go blindly into these endeavors without a way to stop it," said John. "We'd love to provide drug to these patients for the remainder of their lives if it's helping them. But it doesn't usually work that way. There are business decisions behind every plan that we develop. Our strategy defines when we expect these programs to end and why. This is typically centered around the registrational intent for the product and when we expect the product to be approved and reimbursed in those countries."

"Exit strategies are not always based on commercial availability and reimbursement. There are always exceptions and one-off cases, and there are times when we commit to continue treating patients, and sometimes that is forever, but usually it's until the disease progresses. But we have to end these programs at some point."

From a bioethics perspective, what are your thoughts on deciding not to register a drug that is being used under Expanded Access?

"It is okay to end programs as long as there's appropriate communication and full transparency about why programs are ending," said John. "In terms of safety and efficacy, if we have a safety signal, of course, we need to pull the drug back. However, efficacy data is a bit of a problem because we know what it might mean for the pathway and trajectory of a patient's disease, but patients may not fully understand that. Patients may believe that the rescue that they've been waiting for is there. They've all seen great, investigator-targeted headlines that our companies put out about a fantastic new therapy. But when a

AUDIENCE QUESTION

Do you see an uptick in Expanded Access requests happen after trials end from subjects who might have been eligible but did not enroll?

"Yes, we do see an uptick," said Karen. "Any time data is released, if it's positive, we'll see an uptick even the earliest stages, such as Phase I, which most companies would never even consider providing access. Data drives interest, and interest has really ratcheted up in the last 10-15 years with social media. Companies should be ready for that, particularly if you specialize in a rare disease or an area that has a very high medical need."

"People will use social media, like LinkedIn, find out who is responsible for Expanded Access requests and send pictures of themselves with their family," added Andrew. "It stresses the importance of ensuring there is a great decision-making framework in place at companies for these urgent requests."

clinical trial suddenly ends and the Expanded Access drug needs to be cut off, there's that lack of understanding."

"I think that we all have a responsibility when we're enrolling patients to make sure that informed consent is there. We also need a similar type of informed consent when Expanded Access programs are being run to say that we're going to continue this as long as we feel it's efficacious."

"From a patient advocacy perspective, I believe it's okay to remove patients from a drug. I think feeling like we have a responsibility to keep these patients on a drug that we know may not be working is providing misguided hope for those patients that are on drug."

"We do have a responsibility to remove them from that so that potentially they can find other options that are available to them. We don't want to take that hope away, but we want to say, 'Listen, this is not the rescue that you're looking for, and there may be other avenues for finding a rescue.' However, in the rare disease space, we've seen drugs being allowed to patients until there's another available therapy."

Knowing that a person—a child, a parent, or any person in need— is behind every Expanded Access request, how do you take your emotions out of the process?

"We're all humans and it's very difficult to remove yourself, particularly with pediatric patients and infants," said Karen. "Over 14 years, I've had some very heart-wrenching emails, not only from physicians but from patients and parents."

"I don't want you to remove your emotions from a negative decision. I would like you to allow yourself to maintain that sense of humanity because it means that what you're doing every single day matters."

"I do think it comes down to understanding why there is a change and it's really about communication, transparency, honesty with physicians, helping them to better understand why a program may end, and being able to provide some level of support, such as referring to other studies, other products in development, or advocacy groups."

"I would say that I don't want you to remove your emotions from a negative decision," added John. "I would like you to allow yourself to maintain that sense of humanity because it means that what you're doing every single day matters. If you have that heartbreaking feeling when a negative situation arises, it should allow you to celebrate the successes that you see every single day and will make you a better advocate. It will allow you to wake up and be proud of the work that you're doing on behalf of patients around the world. If you have an opportunity to truly feel it on a daily basis, it will remind you that you are human and I think that that's even better."

What piece of advice would you relay to clinical supplies professionals regarding Expanded Access?

"Be flexible," laughed John. "Expanded Access is going to completely surprise you. It's a collaborative effort. Most of the time it works out, and the times that it doesn't, you start to dig a little bit deeper, and you bring in people to go to that next escalation point to see what you can do to accommodate those requests and to have your clinical supply team be able to fulfill those orders."

Should pharma companies pick and choose which countries will be offered Expanded Access?

"We all have a role and responsibility in the work that we do to advocate for open access across the world."

"A pharma company should absolutely pick and choose based on the feasibility of ensuring long-lasting access into those countries," said Andrew. "If they are providing a program in a country like Brazil, it is going to require a certain number of resources for the duration of the lives of those patients. Then those resources are tied up for a certain number of patients in one country. That may negatively impact the research and their ability to put those funds into other programs that may be just as vital for another patient group that is also in need of rescue."

"I think we need to be transparent with patients and healthcare providers about how those decisions were made. We all have a role and responsibility in the work that we do to advocate for open access across the world."

What are your thoughts on collecting data from patients in Expanded Access programs?

"I've seen proposals come across my desk about running an Expanded Access program and collecting 20-25 data points, which would be cumbersome for physicians, patients, and everyone involved," said Andrew. "They are aiming to collect real-world data and evidence to help with the reimbursement of a drug or perhaps fill in the gaps of some of the data that was not there in the clinical trial."

"I think it's okay to collect a few signals as you're going along, such as safety, but there is a balance. If you stray from the idea of a treatment with an urgent need and are moving into clinical trial data, regulators will ask you to open up another arm of the trial."

Looking back on past Expanded Access requests, is there anything that you wish you would have done differently?

"We have been tripped up in the past when making assumptions about what is and what is not permitted in a particular country given the regulatory guidance. As you know, guidance requires interpretation. At the last minute, we have received unexpected updates, for example, when a physician came back to say, 'Actually, the Health Authority said I can't do this, or we need this specific aspect to be able to treat this patient.'"

"I would recommend working closely with a physician and site to better understand if they have experience, especially when working in remote countries where it's not clear what you need to do in terms of documentation and customs. You need to ask if they've ever brought in any unlicensed medicines and encountered any issues—before you proceed."

Where could we have better standardization in Expanded Access?

"Oftentimes we are running a trial with combination therapies using a competitor's product. We have challenges around understanding the regulatory landscape of what we should and should not provide, and when we're obligated to provide it. That's one area where I feel like we need to become stronger, trying to define what we are going to do, and how we are going to do it if it involves multiple products. This comes back to our previous conversations around understanding the landscape where you're going to do the trials and a framework for your Expanded Access."

Do you have a favorite Expanded Access memory that you would like to share?

"I often say you become addicted to the space in compassionate use, because there are so many gratifying moments and wonderful stories, and even to the point where patients will send you pictures of themselves," said Karen.

"One thing that was just absolutely amazing and groundbreaking was our work with a very well-known investigator who genetically diagnosed a baby in utero with a fatal rare genetic disease. It was quite exciting to mobilize based on the country's requirements and consent requirements so that upon the birth of the baby we were able to have the first dose ready. The baby was dosed on day 11. It was gratifying to get these wonderful 'thank yous' from the site, the physician, and even our medical science liaison, who really helped facilitate with the local language."

"I live in Canada, and we have a publicly funded health system that is supposed to help everybody—unless you fall on the wrong side of the genetic lottery and you need a drug that costs $500,000 or more per year," said Andrew. "When my son Isaac was diagnosed at 18 months old, NAGLAZYME®, made by BioMarin, was just approved in the United States. The treatment wasn't approved in Canada, and it wasn't going to come to Canada, because we only had three patients and my son Isaac was the only treatable patient at the time."

"I often say you get addicted to the space in compassionate use, because there are so many gratifying moments and wonderful stories."

"Long story short, after six months of advocacy, and my son being on the front page of our national newspaper, he was able to gain access. We were told that he would live to 12 at the time, and we said we were going to beat that number. NAGLAZYME provided a great lifeboat for him, and we also said that we were going to fund research to get a cure. We put millions of dollars into a gene therapy project out of Italy and Isaac was the fifth patient infused with that gene therapy approach."

"I know every case that I've ever worked on and the advising that I do for companies to make sure that there's a rescue for patients in need. My story with Isaac is still unbelievably special to me."

Learn more about the GCSG Expanded Access Resource e-Team at **https://mygcsg.com/EAP/**

GCSG would like to thank PAM Pharm for co-sponsoring the development of this important industry article.

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