Maximize the Collection of Real-World Data in Expanded Access Programs

Jose Ricardo Perez, MD.
Executive Medical Director
Novartis Oncology
East Hanover, NJ
Disclaimer:

• The opinions expressed in this presentation and on the following slides are solely those of the presenter and not necessarily those of Novartis Pharmaceuticals Corporation (“NPC”).

• NPC does not guarantee the accuracy or reliability of the information provided herein.
Maximize the Collection of Real-World Data in Expanded Access Programs

- Key Definitions
- Supplementing clinical data with Patient Reported Outcomes (PRO)
- The newest digital health applications for electronic data collection (ePRO)
- Are there approaches that have worked or that haven’t worked?
- What processes has FDA approved that have worked successfully?
Key Definitions

• A clinical trial is the preferable route for a patient to receive access to treatment with an investigational product.  
  - allows for generation of adequate safety and efficacy data that may lead to the regulatory approval of the product, hence making it widely available to more patients.

• Where a patient has a serious or life-threatening disease or condition for which all currently available treatment options have been exhausted and enrollment into a clinical trial is not possible

• The request to use an unapproved product for a patient under the ‘Expanded Access’ provision should come from the patient's treating physician and be independent
Criteria:

- An independent request should be received from the treating physician;
- The patient to be treated has a serious or life threatening disease or condition, and no comparable or satisfactory alternative therapy is available to monitor or treat the disease or condition;
- The patient is not eligible to enroll in a clinical trial;
- There is a potential patient benefit to justify the potential risk of the treatment use, and the potential risk is not unreasonable in the context of the disease or condition to be treated;
Utilization of EAPs across the product lifecycle

- EAPs can be used as a mechanism to provide access to product in the following situations:
  - Access to unapproved product during the development phase
  - Access to product approved by major regulatory authority but not in country of request
  - Post-approval access
  - Post-trial access (continued access)
Data Collection in an EAP

• The objective of an EAP is to provide early patient access to products for the treatment of a serious or life-threatening disease or condition.

• While the primary purpose of an EAP is not to collect data, some information should be obtained on the use of the product by a patient.

• Safety data should be collected, while other information such as treatment duration, dosing, patient demographics, and in some cases a simple measure of effectiveness (minimal) could be collected in an EAP.

• In case of a treatment for a rare disease, there may be a benefit in capturing select outcome data that supports further understanding of the new product within the small patient population.
Supplementing clinical data with Patient Reported Outcomes (PRO)

• **Oncology PROs: Limited Use Due To Small Trials, Fast Drug Development**
  
  – Patient-reported outcomes in oncology clinical trials remain an infrequently used tool, despite acknowledgement by sponsors that the patient experience is important to measure – and encouragement from FDA officials to do so.
  
  – The lack of PROs in oncology may be a byproduct of the fast pace of cancer drugs are developed in the U.S.: small trials and accelerated pathways.

• PROs are growing in importance in drug development, because they help inform patients on how they may react to a treatment regimen.

• FDA’s patient-focused drug development initiative has pushed that agenda, but oncology has lagged behind other areas of pharmaceutical R&D in prioritizing the patient experience by including PROs in clinical trials – and including them in approved labeling.

• Without PROs, advocates say, a critical piece of drug development is lost.

https://pink.pharmamedtechbi.com/PS079922/Oncology-PROs-Limited-Use-Due-To-Small-Trials-Fast-Drug-Development
Patient-Reported Outcomes Labeling for Products Approved by the Office of Hematology and Oncology Products of the US Food and Drug Administration (2010-2014)

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Oncology NMEs and BLAs Approved</th>
<th>No. of Oncology Products With PRO Labeling</th>
<th>No. of Nononcology NMEs and BLAs Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>2</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>2011</td>
<td>8</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>2012</td>
<td>12</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>2013</td>
<td>9</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>2014</td>
<td>9</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Total (2010-2014)</td>
<td>40</td>
<td>3</td>
<td>120</td>
</tr>
</tbody>
</table>

Abbreviations: BLA, biologic license application; FDA, US Food and Drug Administration; NME, new molecular entity; OHOP, Office of Hematology and Oncology Products; PRO, patient-reported outcome.

Results
- Of 160 drugs approved by the FDA (2010-2014), 40 were approved by OHOP.
- Three (7.5%) of the 40 received PRO-related labeling (abiraterone acetate, ruxolitinib phosphate, and crizotinib).
- Compared with nononcology drugs (2011-2014), oncology drugs were more likely to be orphan and first in class.
- The majority of oncology drug reviews by FDA were fast track, priority, or accelerated.

Conclusion
- Although symptoms and functional decrements are common among patients with cancer, PRO labeling is rare in the United States, likely because of logistical hurdles and oncology study design.
- Recent developments within the FDA OHOP to capture PROs in oncology studies for the purpose of product labeling are encouraging.
Conclusions

• Clinical outcome assessments, such as PRO, can provide important data to support the safety and efficacy of a cancer treatment.

• We should expect a similar degree of scientific rigor to be applied to the PRO strategy as is expected in assessing conventional measures such as radiographic tumor assessments.

• Individual measurement of patient-reported symptomatic adverse events, physical function, and disease symptoms provides important patient-centered data on key components of HRQOL and may be more sensitive to a therapy’s effect on the disease and the patient.

• Rigorous patient-focused symptom and function data are needed in cancer clinical trials, and it is critical that we reevaluate available tools and practices to carefully select the most important concepts to measure, and measure them well.
The newest digital health applications for electronic data collection (ePRO)

http://medcitynews.com/2016/05/7-technology-trends-will-revolutionize-electronic-patient-reported-outcomes-assessments/
The newest digital health applications for electronic data collection (ePRO)

- Consumerization of User Experience
- Move to the Cloud
- Real-time Insights & Feedback
- Rise of Mobile and Tablets
- Bring Your Own Device (BYOD)
- Wearables & Devices Integration
- Big Data

http://medcitynews.com/2016/05/7-technology-trends-will-revolutionize-electronic-patient-reported-outcomes-assessments/
The newest digital health applications for electronic data collection (ePRO)

Pro:
1) Time
2) Quality of the data
3) Analysis
4) Excitement about technology

Cons:
1) Cost
2) Age – Access restriction
3) Time per tool & overall number of tools

http://medcitynews.com/2016/05/7-technology-trends-will-revolutionize-electronic-patient-reported-outcomes-assessments/
PROs in EAPs

Can PROs be used?

Yes

Did you use them in your registration trial?

Yes

Conflicting Results Risk

No

Include Them in your EAP design

No

Phase IIIb trial
Do we need to modernize EAPs?

• Modernization of Clinical trial Eligibility:
  – % of Patients participating in clinical trials
  – Exclusion of patients with: brain metastasis, minimum age, HIV/AIDS and organ dysfunction

• Real World Evidence:
  – Use of Electronic Health Records
  – Improving data capture, quality and analytics

• Exploratory Randomized trials:
  – Expand the exploratory randomized trial, if survival benefit is maintained, seek regulatory approval
  – Exceptional Survival data in an exploratory trial may lead to regulatory submission and initiation of a phase III confirmatory study
Are there approaches that have worked or that haven’t worked?
Access to Unapproved Drugs: FDA Policies on Compassionate Use and Emergency Use Authorization

Susan Thaul. Specialist in Drug Safety and Effectiveness August 4, 2015
FDA’s expanded access procedure

- a licensed physician, may request access to an investigational drug—through either a new IND or a revised protocol to an existing IND—if:
  - a licensed physician determines
    - the patient has “no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat” the serious disease or condition; and
  - “the probable risk to the person from the investigational drug or investigational device is not greater than the probable risk from the disease or condition”; and
  - the Secretary determines
    - “that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug” for this person; and
    - “that provision of the investigational drug … will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval”

Susan Thaul. Specialist in Drug Safety and Effectiveness August 4, 2015
FDA vs. right to try: Our view

The deadly Ebola outbreak spreading through Africa is so extreme, it is driving health officials to do something that they would instinctively resist in normal circumstances. Subject patients to unproven experimental drugs.

The drugs are risky. Some have not even been tested on humans. Even so, a World Health Organization ethics committee just declared such use ethical, and its reasoning is hard to dispute, at least for patients who would otherwise die. Some chance is better than none, even with unknown side effects.

Too bad American patients suffering from terminal illnesses have so much trouble getting the same chance.

FDA is not the main problem: Opposing view

Suppose that you found out your son or daughter was dying of an untreatable brain tumor. Suppose you also found out that a pharmaceutical company was working on a drug to treat that disease but that it had only been tested in 10 adults.

While all the patients came through unharmed, only two showed a little improvement. If your doctor said that drug was your child’s only hope, but the Food and Drug Administration (FDA) might not let you get it, wouldn’t you want something done?

That is exactly what state “right to try” laws seek to do. The problem is that the FDA is not the main obstacle standing between desperately ill people and experimental drugs.
What processes has FDA approved that have worked successfully?

• Under FDA’s current regulations, there are three categories of expanded access:
  – Expanded access for individual patients, including for emergency use
  – Expanded access for intermediate-size patient populations (generally smaller than those typical of a treatment IND or treatment protocol)
  – Expanded access for widespread treatment use through a treatment IND or treatment protocol (designed for use in larger patient populations)

• For each category of expanded access, there are two types of regulatory submissions that can be made:
  – an expanded access protocol submitted as a protocol amendment to an existing IND (i.e., an expanded access protocol) or
  – a new IND submission, which is separate and distinct from any existing INDs and is intended only to make a drug available for treatment use (i.e., an expanded access IND).

The expanded access submission must include:

- A cover sheet (Form FDA 1571);
- The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;
- The criteria for patient selection or, for an individual patient, a description of the patient’s disease or condition, including recent medical history and previous treatments of the disease or condition;
- The method of administration of the drug, dose, and duration of therapy;
- A description of the facility where the drug will be manufactured;
- Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;
- Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and
- A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

The information on this page is current as of April 1 2016
FDA decisions:

• Approved use for a new drug
• Unapproved use of a drug that FDA has approved for another use
• Unapproved use of an investigational new drug
• Unapproved use of a product that has not yet begun clinical testing
FDA authorizes over 99% of expanded access requests it receives

An analysis of common ethical justifications for compassionate use programs for experimental drugs

• The most frequently voiced justifications for compassionate use or expanded access programs could be put in one of three categories:
  – justifications of justice:
    – where compassionate use programs could be seen as a just or fair way to distribute experimental new drugs to patients who are denied access to RCT's through no fault of their own
  – ethical principle of beneficence:
    – where it could be claimed that terminally ill patients stand to benefit greatly at very little risk (as they are already dying)
  – considerations of autonomy:
    – where, it is claimed, patients should be able to exercise their autonomy and have access to such drugs if that is their free choice and they are fully aware of the risks associated with that choice.

• all justifications are potentially problematic. If they truly form the basis for justification, compassionate use programs should be designed to maximize justice, beneficence and autonomy
Maximize the Collection of Real-World Data in Expanded Access Programs

- Key Definitions
- Supplementing clinical data with Patient Reported Outcomes (PRO)
- The newest digital health applications for electronic data collection (ePRO)
- Are there approaches that have worked or that haven’t worked?
- What processes has FDA approved that have worked successfully?
I've been a cook all my life, but I am still learning to be a good chef. I'm always learning new techniques and improving beyond my own knowledge because there is always something new to learn and new horizons to discover.

Profession: Chef
Nationality: Spanish
Born: July 13, 1969