Ethical Decision-Making for Early Access to Investigational Medicines in Rare Disease

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1. INTRODUCTION

The rapid development of orphan drugs to treat Lysosomal Storage Disorders (LSDs) has created ethical tensions between the need to conduct robust clinical trials and the desire from patients to gain access to these breakthrough therapies outside the traditional clinical trial environment. Early Access (EA) to investigational medicines offers a potential lifeline for patients suffering from a serious or life-threatening condition who have exhausted comparable or satisfactory alternative therapeutic options and are not eligible to enter a clinical trial. However, pharmaceutical companies considering providing EA face several ethical challenges that need to be considered prior to opening an Early Access Program (EAP).

The decision-making process on when to open an Early Access Program (EAP) is complex and can be difficult for pharmaceutical companies to navigate. Early planning is crucial to ensure a clear, transparent, and defensible process is implemented and balances the needs of all stakeholders, including patients and their families, future patients, and the pharmaceutical company. Additionally, careful consideration of the ethical hurdles that EAPs may face is paramount for a successful program.

To help inform the overall process with which programs are considered, created, and opened, a decision-making framework has been designed that incorporates both the ethical principles that ought to be considered and operational aspects that should be at the forefront of EAPs for orphan conditions.

2. GUIDING PRINCIPLES

To conduct this process in the most ethically sound manner, the framework needed to be built starting from a position of "EA will be provided if very specific conditions are met." This starting position takes the burden away from the patient and family, who often must convince a pharmaceutical company to provide access and shifts it to the pharmaceutical company . This also ensures that patients remain at the forefront of the decision, with a commitment to embark on identifying and removing hurdles with a constructive and ambitious mindset. This does not mean all requests are granted but simply means a "yes" is the default unless significant hurdles exist that make access unattainable. If all hurdles identified can be rectified, access can be granted to patients and an EAP created. If hurdles can't be overcome, transparency as to what those hurdles are and why access can't be granted is paramount to the process for both the patient community and the company. An assessment can then be made on when to next review the framework and where possible, provide a time frame of reaching "yes".

3. KEY STAKEHOLDERS

It is important to include all relevant stakeholders in the decision-making process as early as possible . Key stakeholders include Medical Affairs, Regulatory, Commercial, Clinical Development, Pharmacovigilance and Patient Advocacy.

It is also vital to include the community by collaborating with patient and physician community representatives to ensure that patients remain at the forefront of the decision process. If EA is to be provided, it will be done in an ethical and patient focused manner. However, if EA is not to be provided, the decision will have been made collaboratively with transparent communication, managed expectations, fostering a positive relationship between the pharmaceutical company and the community.

4. DECISION-MAKING FRAMEWORK

The decision-making framework was created to provide a structure approach to enable a thorough review of specific treatments in clinical development to determine the timepoint at which EA might be provided .

Hurdle	Considerations
Benefit-Risk Assessment and Clinical data	•Required level of certainty around benefit-risk ratio •Threshold can differ depending on disease severity, disease progression, level of unmet need
Clinical Trial Impact	•Only eligible for EA if enrolment in clinical trial is not possible • Possibility of access alongside placebo-controlled trial
Country Scope and Commercialization	•Equity of access for broader population •Market access considerations for long term continuation of access •Access to centres of excellence if required •Clear exit strategy required
Patient Scope Rationale and Drug Supply	•In line with trial population or broader? •Sufficient supply for current and future trials plus EA •Build into manufacturing forecast as early as possible
Costs and resources	•Financially resourcing an EAP should not be at the expense of other clinical development programs •Consider internal resource as well as cost
Community Impact	•Balance of true global equity and achievable access •Patients as partners, through early, frequent and transparent discussions with patient community
Ethics	•Consideration of the broader patient community need to be balanced with the individual patient needs
Timelines and Exit Strategy	•Exit strategy is needed for all countries in scope •Transparency with community

5. CONCLUSION

Starting from a position of "yes", engaging with the community, and following the decision-making framework allows the pharmaceutical company to incorporate the valuable input from different patient populations and key opinion leaders into their decision. Through a transparent process, the framework accounts for the desire or need for EA through external engagement and the feasibility of EA from the pharmaceutical company perspective.

References

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