Developing a Decision-Making Framework for Expanded Access to Gene Therapy in Rare Neuromuscular Diseases

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1. INTRODUCTION

Expanded access (EA) to investigational medicines offers a potential lifeline for patients suffering from a serious or life-threatening disease, who have exhausted other comparable or satisfactory alternative therapeutic options and are not eligible to enter a clinical trial. The 21st Century Cures Act requires that a company developing investigational medicines should make a policy regarding EA public and readily available. Navigating through EA can be challenging due to a number of considerations, such as the stage of clinical development, the safety profile of the investigational medical product (IMP), commercialization plans and the needs of different stakeholders. The aim of this work was to develop a decision-making framework on EA to a gene therapy for a rare neuromuscular condition, keeping the patients and families at the centre of this process.

2. METHOD

To implement a patient-centric decision-making framework, we started from a position of "yes, EA will be provided if very specific conditions are met". A landscape analysis was carried out to determine the current barriers, including some specific to gene therapies, and interviews were conducted with external stakeholders, including Patient Advocacy Groups (PAGs) and Key Opinion Leaders (KOLs), to establish the current needs and desires of the community. Patient profile case studies were developed, and the potential barriers and community needs overlayed using a decision-making framework to ascertain whether EA was possible at this time point. This method allowed for ample reasoning, transparent rationale, and honest reflection on whether to provide EA to eligible patients.

3. COMMUNITY ENGAGEMENT

In order to navigate these hurdles, it is vital to turn to the community by collaborating with PAGs and KOLs 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 and foster a positive relationship between the pharmaceutical company and the community. PAGs and KOLs provide invaluable insights into the realities of the disease and thus should included in the clinical development process, which would encompass EA.

The hurdles and considerations around EA are outlined in Table 1, where the first and more important one is the risk:benefit ratio. In a life-threatening condition such as a rare neuromuscular disease, the threshold for this ratio is often lower as patients may be more inclined to take higher risks due to the high unmet need. However, as this is for a GT, the threshold can increase significantly due to the unknowns around long term safety and efficacy.

Table 1: Hurdles and considerations for Expanded Access

Hurdle	Considerations
Risk:benefit ratio	•Safety over efficacy •Consider risk of not providing access •Patient segmentation based on benefit: risk
Clinical Expertise	•Can the treatment be administered to standards expected by both sponsor and KOL's (e.g., capability, capacity)? •Can safety be effectively monitored? •Is appropriate follow up care available?
Logistics	•Are logistical capabilities available in all countries? If yes, is there sufficient time is available to plan for a global program that is as equitable as possible?
Commercial Sustainability	•Deep dive into commercial plans (countries/timelines/patient population sizes/pricing strategy)
Manufacturing	•How much product would be needed? •If stock levels are limited, consider ethics of providing to only small percentage of a patient population versus the majority

4. EXPANDED ACCESS (EA) to GENE THERAPY (GT)

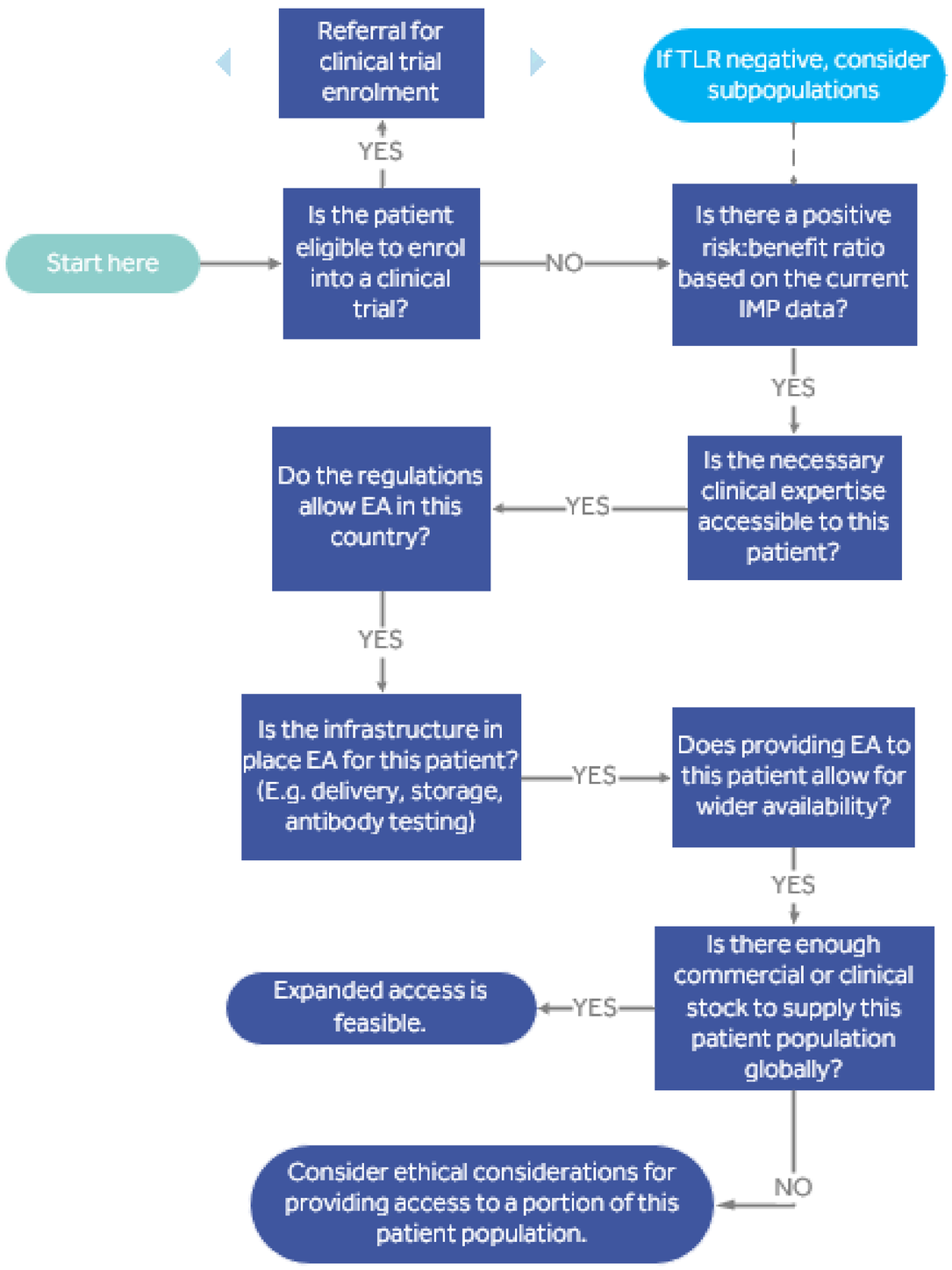
In addition to the challenges around EA described , gene therapy (GT) comes with its array of considerations, outlined in Table 2.

Table 2 considerations for pre-approval access to gene therapy

EA Consideration	GT Consideration
Clinical trial eligibility (Inclusion/exclusion criteria)	EA for one-time treatment may impact eligible population
Potential for data collection	All data is valuable as opportunities for collection are limited
Risk-benefit analysis (Is the current level of safety/efficacy data adequate)	Long term safety often unknown, long term follow up required
Sufficient supply is required for clinical development and EA	Complex manufacturing
Complex administration and follow up	Need for experienced expert centres with GT infrastructure

The established decision-making framework, showed in Figure 1, combines the challenges around EA, GT and additional considerations from the pharmaceutical company perspective. This framework is specific to gene therapy in rare neuromuscular diseases but could be adapted to other IMPs and disease areas where EA is considered.

Figure 1: Expanded Access Decision Making Framework



5. CONCLUSION

Starting from a position of "yes" engaging with the community and following the decision-making framework enabled a clear patient-centric approach. The inclusion of the different needs of Patient Advocacy and Key Opinion Leaders were of significant value as, in this case, the community was not in favour of EA at this time and preferred resources to be allocated to long term equity of access, a position that had not been predicated prior to external engagement.

References

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