**Challenges to Orphan Drug Development**

1. **Lack of an animal model**
   - That shows similar signs/symptoms to a human with the disease (or, at minimum, shows signs/symptoms that can be measured and tested).

2. **Control Group not possible or ethical**
   - For very rare, rapidly progressive, fatal diseases, there may not be sufficient patients for controlled trials, and there can be ethical concerns with having placebo controls in clinical trials. In these cases, data on the natural course of the disease that are collected outside the trial may be used for comparison.

3. **Poor understanding of the natural history**
   - Of many rare diseases (e.g., clinical features, progression, signs and symptoms) means it is difficult to develop new therapies, design clinical studies and determine an appropriate trial duration.

4. **Lack of appropriate endpoints**
   - (e.g., lab values, patient-reported outcomes (PROs), clinical exams/assessments, etc.) available for a clinical trial to show that a therapy is effective.

5. **Very small numbers**
   - Of people with each orphan disease leading to challenges recruiting enough patients to participate in trials.

6. **Challenges securing Government & Insurance Company Reimbursement**
   - For very expensive therapies.

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**Cost of Development**

- **Orphan**: ~$291M
- **Standard**: ~$412M

Cost per patient of orphan drugs is high because there are fewer patients being prescribed orphan drugs when compared to “standard” therapies, meaning that fewer patients are available to cover the cost of development. (Jayasundare et al., 2019)

**Additional Resources**

- **Cost of Orphan Drugs vs Standard Drugs**: https://ojrd.biomedcentral.com/articles/10.1186/s13023-018-0990-4
- **Global Genes Resources**: https://globalgenes.org/resource-hub/
- **Why do Discovery and Development Take so Long?**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5723284/