Pediatric Cholestasis Working Group

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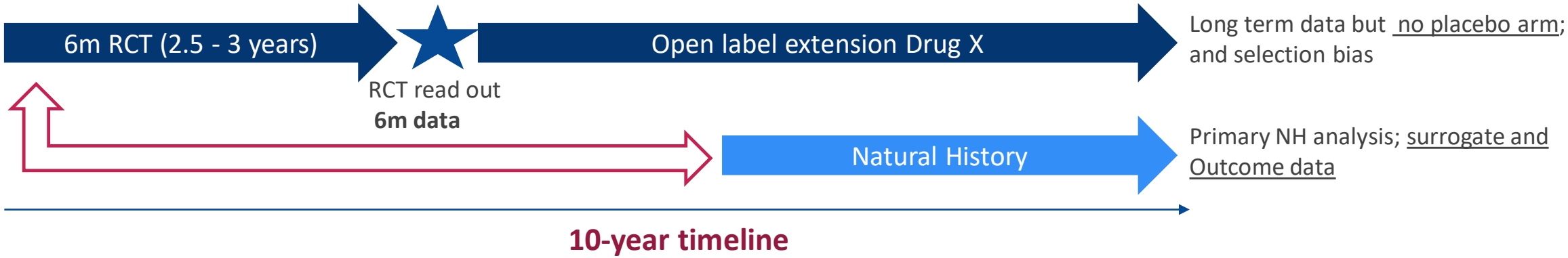
Industry Perspectives on Natural History Registries

Industry Challenges

- **In ALGS and PFIC placebo-controlled studies to date consist of a maximum of 6-month primary endpoints**
- **Hard clinical outcomes are only observed after several years, but longer-term placebo-controlled studies are not feasible**
  - Retention, recruitment and ethics around long-term placebo arms
  - Can continue to collect outcome observations for years, but absence of long-term comparator arm
- **How do we provide comparative outcome data for a treatment without running the impossible several years-long placebo controlled randomized study?**
- **The timelines for studies must overlap with useful information over the same timeline from natural history data**



Natural History Registries are Critical and Imperfect

- **Natural history registries are critical in rare diseases, providing opportunity to further understand the disease**

- **Global accumulation of patient history = larger numbers and more comprehensive view of disease not possible in a clinical trial**

- **NH registries are not prospectively planned for regulatory submissions**
  - Cannot be prospectively planned for future treatment comparisons
  - There will be gaps in what has been collected in the past and what is required in the future
  - NH registries are imperfect but there are paths for treatment comparisons

Utility of NH Registries and FDA Guidance

- **Strengths of a global natural history registry :**
  - long term (decades) clinical data, large numbers of patients, capture of hard outcomes
  - Identification of critical surrogate markers that can predict response and event free survival

- **NAPPED and GALA exist! The only global registries with decades of retrospective data**
  - Robust global data collection and verification
  - Broad geographic variety of centers which overlap with clinical trial centers

- **FDA DRAFT Guidance for Industry in Rare Diseases: Natural History Studies for Drug Development:**

"Regardless of external control type, even for diseases with relatively predictable progression, an external control is most interpretable when a treatment effect: (1) is large in comparison to potential biases and the known variability in progression, (2) is not affected by patient or investigator motivation or choice of subjects for treatment (3) can be objectively measured, (4) is measured in a manner that reasonably manages and minimizes bias, (5) has a strong temporal association with administration of the investigational drug, and (6) is consistent with expected pharmacological activity based on the target and perhaps shown in animal models

Industry Perspective – Challenges of Natural History Comparisons

- **Industry goal in a NH comparison is to be able to compare long-term hard clinical outcomes of a treatment vs the natural course of the disease, providing a long-term "control" group**

- **Limitations include gaps in data and differences among centers:**
  - Timing of data collection
  - Laboratory reference ranges
  - Parameters that are measured regularly at certain centers and not at others
  - Standard of care variability
  - No consistent way to record patient reported outcomes, such as severity of pruritus

- **Regulators may require the natural history data as part of a filing – what are the considerations from all stakeholders particularly from the Natural History Study Groups?**

Industry Perspective – Considerations of Natural History Comparisons

- **Regulatory agencies are approached by companies when treatments are available, and not by academic parties at the time a registry is generated, therefore, NH data collection cannot be prospectively identified or collected for inclusion into a future comparative analysis**

- **A well-selected, appropriate cohort must be identified, which is representative of the treatment population - Key considerations:**
  - Eliminate potential bias,
  - Add independence of analysis,
  - Pre-specified SAP (cohort selection process, statistical methods, sensitivity analyses)
  - Evaluate comparability of study populations

- **Company efforts to collect follow-up data from discontinued clinical trial patients for a comprehensive outcome analysis**

Where do we go from here?

- **How best do we engage each other/key stakeholder groups to tackle these rare diseases?**

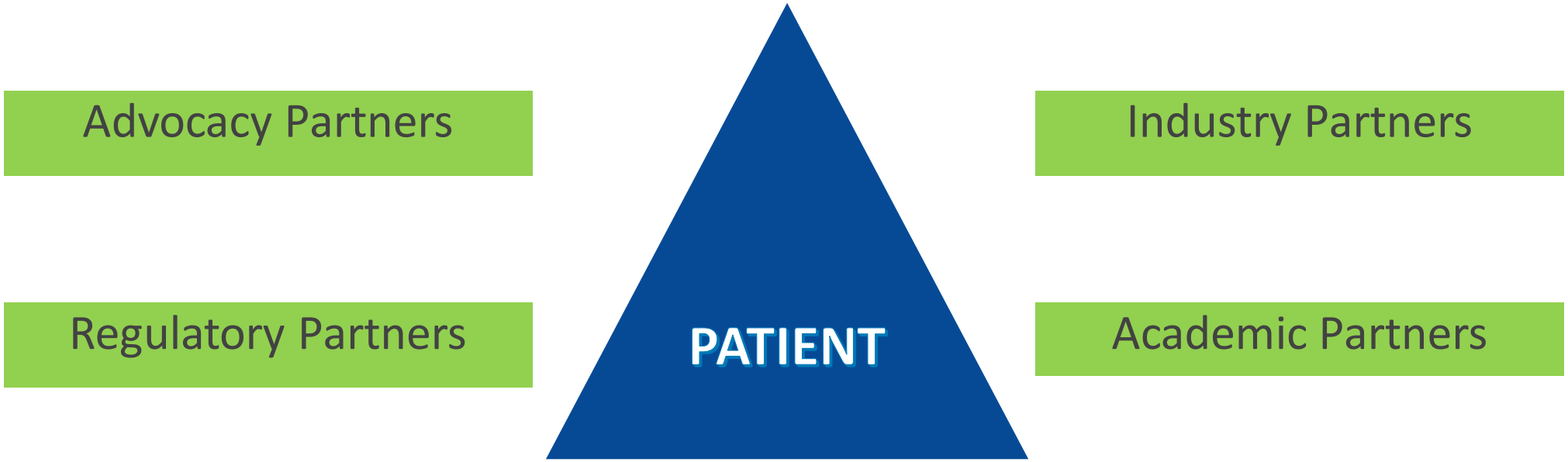
- **What about other diseases with even fewer patients (ultra rare)?**

- **Define the minimal and reachable needs for regulatory submissions and approval**
  - Considerations should be applied to rare diseases that are not applied to larger well-knows indications

Key opportunity to understand current/future therapeutic targets using NH data, starting with PFIC and ALGS

Overarching Goal of this Working Group

To improve the lives of children with rare liver diseases each group has a responsibility



Next Steps: Inclusive “round table” approach to incorporate input from all stakeholders

Questions and Discussion