National Brain Tumor Society

July 16, 2021

"Use of External Control Arms in Pediatric Brain Tumor Trials"

The seventh Research Roundtable took place on July 16, 2021, as a multi-stakeholder, multi-disciplinary group of distinguished pediatric brain tumor experts, statisticians, industry leaders, regulator officials and patient/caregiver representatives convened for a half-day virtual session meeting focused on use of external control arms in pediatric brain tumor clinical trials.

Roundtable participants discussed key issues and opportunities in leveraging external datasets to expedite conduct of pediatric brain tumor studies. Participants also engaged in small group breakout sessions to discuss incorporating external control data in one potential test case—Diffuse Intrinsic Pontine Glioma (DPIG). The objectives for the meeting were to discuss considerations and potential consensus criteria for using external controls in pediatric brain tumor clinical trials. Key topics to be considered included: identifying data sources; defining ways to validate the data; evaluating trial design approaches to incorporate external control the data; and identifying and advancing action steps, including considerations for developing a pediatric neuro-oncology pilot in DIPG.

Key themes and key takeaways for the pediatric brain tumor community that emerged included:

- The status quo for pediatric brain tumor treatment is unacceptable; new ways of conducting clinical trials are urgently needed.
- Patients and families support the idea of leveraging the power of data and welcome increased opportunity to access experimental therapies in clinical trials.
- While the gold standard for registration clinical trials remains a randomly controlled clinical trial, meeting this standard is difficult in rare tumor types and settings where there is no good standard of care option for patients.
- The approach of using external control data to advance clinical trials in the regulatory environment requires careful upfront planning, fit-for-purpose data, an assurance that the control data being used match with the population under study, and as much patent-level data as possible.
- Multiple data sources are relevant for developing an external control arm, including real-world data (e.g., data form electronic health records, administrative claims data,

registries, patient-generated data, or environmental data), prior clinical trial data, literature-based based, and synthetic data. Creating standard common data elements would be valuable.

- It is important to aim for larger effect size when using external control data. It is not possible to look for a 10% change in survival because that is going to be within the variability of the historical data. Additionally, there is a need to focus on futility and plan for interim analyses that would allow the termination of a trial that is not successful as early as possible.
- Adaptive trial designs and Bayesian approaches may be useful in incorporating external control data, including through hybrid trial designs that allow for some concurrent controls that can be compared with the external control dataset.
- Non-registration studies can be developed and conducted with the goal of generating the type of data that can be useful as external control for future registration studies. It is therefore important to develop a standardized approach for single arm studies, using similar endpoints and evaluations.
- Centralization of all single arm study data (including those from negative studies) in a way that all sponsors can access would be an important improvement moving forward. Additionally, it is important to gather and annotate non-protocol-based data, including registry data.
- The willingness to share data exists within the pediatric neuro-oncology community, but there are issues to resolve in terms of funding, providing appropriate sustainability, and address intellectual property issues, as well as ensuring that real time sharing of clinical outcome data is harmonized with eligibility and outcome information.
- There are funding needs to be met, especially in supporting the requirements that are being placed on statisticians and clinicians within academic institutions to align on the optimal methodological approaches that can turn existing data into evidence for clinical trials and regulatory review.
- Sponsors and academic investigators should engage regulators as early as possible and in all relevant efforts to develop and use external control datasets to ensure that these approaches will be able to meet the bar if the data are used within a regulatory context.