Memorandum

Date:	3/9/2021
Subject:	Critical Path Innovation Meeting: Embedding Qualitative Patient Interviews in Neurofibromatosis Clinical Trials to Facilitate Drug Development
Date of meeting:	2/5/2021
Requestor:	Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration

Note: Discussions at Critical Path Innovation Meetings are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants.

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CDER, OND, Division of Clinical Outcome Assessments
CDER/OND/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine, Division of Rare Disease and Medical Genetics
CDER/OND, Office of Oncologic Diseases

Requestor Representatives:
Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration

1. BACKGROUND

REiNS (Requestor) is an international consensus effort that began in 2011 to develop standardized criteria for determining treatment response in patients with the rare, neurological diseases of neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), and schwannomatosis. Patient-centered assessment of treatment benefit in rare disease clinical trials is often limited by a lack of validated clinical outcome assessments (COAs), clinical heterogeneity, and small sample sizes that limit the ability to detect statistically significant changes. Qualitative interviews with rare disease patients enrolled in clinical trials can supplement traditional quantitative assessments to provide a holistic, patient-centered view of the risks and benefits of new treatments. This CPIM is being requested to discuss this mixed-methods approach to clinical trial analysis for rare diseases.

2. DISCUSSION

Requestor provided an overview of the organization and of NF1, NF2, and schwannomatosis. The challenges associated with measuring NF and examples of NF clinical trials were discussed. Applications of

qualitative data in drug development were described and instances where qualitative data has been successfully utilized in trials were provided.

The FDA applauded Requestor's holistic approach to understanding benefit in patients with NF and noted that qualitative data can be very important across the spectrum of identifying conceptual disease models and interpreting measures. Understanding the mechanism of action (MOA) of the agent being studied is important to assessing if the endpoint being prioritized shows response to the treatment. It is important to obtain a good sampling of patients across the target population with respect to factors such as age and location of tumor. With respect to developing instruments, patient and caregiver input should be used to develop fit-for-purpose clinical outcome assessments (COAs). During the development phase, it is important to understand if response options in COAs are meaningfully different than patient perspectives. Qualitative methods, such as exit interviews can be useful for interpreting meaningful within-patient change.

There was discussion on the potential for conducting individual endpoint analyses by combining concepts of clinical benefit based on categories such as tumor location. A well-thought-out plan should be developed before implementing such an approach. The lack of blinding can be problematic. A holistic approach that correlates the COA with actual tumor measurements can also be considered. In oncology, patient-reported outcomes (PROs) are typically used for safety or tolerability. In an efficacy study, blinded, randomized trials are stronger evidence for use of subjective endpoints. In a randomized design, stratification on the basis of individual endpoints would be challenging because of the number of stratification factors, but the FDA would need to see a detailed protocol to make this determination.

With respect to using outcomes such as range-of-motion in combination with qualitative factors, improvement of function should be demonstrated using robust, multi-dimensional analyses. Benefit can be demonstrated using several key measures that all go in the right direction.

There was discussion on when qualitative data should be collected. This schedule is highly context-dependent. A long trial may be associated with reduction in data quality. In an efficacy trial, the PRO should be tailored to when tumor shrinkage is expected to occur. FDA noted that although tumor size does not correlate with benefit in all cases, there should be some evidence of tumor shrinkage or delay of tumor progression with a treatment that has an anti-tumor MOA. The FDA noted that in order to maintain trial integrity and blinding, qualitative research is typically not performed during an ongoing trial. Much information can be obtained outside of a clinical trial. A caregiver of a child with NF1 noted that waiting until a trial is concluded to collect qualitative data may present challenges because young children may have difficulty remembering the information.

There was discussion on how qualitative data can be used to understand treatment harms and to manage side effects. A patient representative noted that quantitative measures do not accurately capture benefit or side effects such as tinnitus or dehydration. FDA noted that individual patients with the same disease that are on the same drugs have vastly different experience regarding what is clinically meaningful to them and establishing uniformity in how this information is captured and reported is extremely important from a regulatory standpoint.

With respect to trial design, randomization is challenging for very rare diseases. The FDA evaluates the totality of the data to determine if a drug works for the mechanism proposed and qualitative data can have a role in that assessment. FDA encourages discussion of specific protocols that incorporate use of qualitative data and is willing to provide feedback on such designs. FDA is also willing to review the

structure of interview questions to capture the aspects of the patient experience that would be most helpful in a drug development package.

The Requestor and FDA noted that they are both open to engagement with other rare disease groups for the purpose of sharing data and information and discussing challenges and opportunities that may exist.

3. ADDITIONAL RESOURCES AND NEXT STEPS

- FDA Guidance on Patient-Focused Drug Development can be found here.
- Duke-Margolis meeting summaries on Establishing and Interpreting Meaningful Within-Patient Change can be found here.
- The Office of Oncologic Diseases is open to having more structured discussions regarding use of qualitative data in the context of a specific drug development program.