Clinical Outcome Assessments in Brain Tumor Clinical Trials: Summary of a Jumpstarting Brain Tumor Drug Development Coalition Workshop

Objective:
To summarize the discussion sessions in the Brain Tumor Clinical Trial Endpoints Workshop on Clinical Outcome Assessments (COAs) held on October 15, 2014 in Bethesda, MD.

Workshop Overview:
The Jumpstarting Brain Tumor Drug Development Coalition (which includes the National Brain Tumor Society, Accelerate Brain Cancer Cure, Musella Foundation for Brain Tumor Research and Information, and Society for Neuro-Oncology) sponsored two workshops to evaluate the state of the field and improve, as well as clarify, the use of brain tumor related clinical trial endpoints, with a goal of advancing the development of treatments for glioblastoma (GBM). The workshops brought together stakeholders from all aspects of the brain tumor community, including clinicians, researchers, industry, patients and patient advocates, the National Cancer Institute (NCI), and the Food and Drug Administration (FDA)[1]. It is the hope of the Jumpstarting Brain Tumor Drug Development Coalition that the workshop and post-workshop actions will stimulate and increase interest and capacity to pursue clinical trials seeking FDA approval of new therapies. The summary of discussions and action items from the workshops are meant to inform and guide the neuro-oncology and clinical trial sponsor community.

The first workshop was held in January 2014 and primarily focused on clinical trial endpoints measured by radiographic imaging. The second of these workshops, and focus of this summary, was designed to afford the brain tumor community a better understanding of what it will take to improve measurement of COA endpoints and optimize these measures to advance their inclusion into adult primary brain tumor clinical trials evaluating therapeutic agents. The discussions also sought to identify specific, practical action plans to develop new measures, as well as increase the use of existing COA endpoints in future brain tumor clinical trials.

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[1] The Jumpstarting Brain Tumor Drug Development Coalition recognizes the participation of the FDA in the planning and implementation of the workshop. We are grateful for the time, expertise, and interest of the FDA's planning team to help make the workshop successful.

Specifically, stakeholders: 1) identified multiple concepts of interest addressing both how a patient feels and how the patient functions, and began determining which sign(s), symptom(s), and function(s) are of priority to patients, and which can be measured in a clinical trial setting; 2) examined COAs that are available for use now in brain tumor clinical trials, and determined the priorities for refinement of the existing measures and necessary elements needed for development of novel COAs for future use in trials; and 3) defined how the COA will be used to determine clinical benefit and recommended clinical trial designs for COA validation and use in brain tumor patients.

The workshop, moderated by Dr. Clifford Goodman[2] of the Lewin Group, began with a formal presentation by Dr. Paul Kluetz of the FDA to establish context for the day's discussions, titled "Use of Clinical Outcome Assessments in Oncology: Successes and Pitfalls." Following Dr. Kluetz's presentation, the workshop continued with four panel discussions. The panels consisted of experts in neuro-oncology and COAs, including FDA staff, industry representatives, medical/academic researchers, and patients. After a short overview presentation by each panel, a facilitated audience question and answer session followed. The panel discussions and central questions are summarized below. The panel discussions were supplemented by formal presentations by FDA representatives throughout the day on such topics as: "What Can Be Learned from the FDA PRO Guidance?" and "Regulatory Experience with COAs and its Relevance to Brain Tumor Studies."

Panel Central Questions
Panel 1: • Toward an endpoint priority list: What are the signs and symptoms and performance-based attributes of brain tumors that are both important to patients and are important to drug sponsors to include in clinical trials seeking FDA approval? • What is the role of steroids or the reduction of the use of them as a potential endpoint? • Considering the heterogeneity and neurological as well as oncological aspects of brain tumors, what are the pros/cons of single symptom, multiple or domain-based symptoms or a functional approach to clinical benefit? • Working List: Some signs and symptoms may be related to the disease, the treatment, or both. How do you consider these signs and symptoms and what about the impact of treatment signs and symptoms on the disease? How do you identify signs and symptoms in trials? Does it matter if it is a low-grade or high-grade glioma?
Panel 2: • What are the COAs available for use in therapeutic clinical trials for

[2] The Jumpstarting Brain Tumor Drug Development thanks Dr. Goodman for moderating both the January and October 2014 Endpoints Workshops.

patients with malignant gliomas for each of the priority concepts of interest? • What is the preferred COA type for each concept of interest? • What are the properties by which COAs should be assessed to justify their use as an endpoint for studies designed to assess the anti-cancer activity of experimental drugs? • What is the role of COAs in assessing toxicity of treatment in patients with malignant glioma? • Is the neuro-oncology community aligned with the FDA's Office of Hematology and Oncology Products in regard to the importance of clinical outcome assessments that reflect proximal, glioma-related endpoints? • Where is there need to develop new COAs for patients with malignant gliomas?
Panel 3: • What criteria should be used to decide if COAs are appropriate for a clinical trial? Is it based on phase of trial? Randomized? Proposed status of the COAs (primary, secondary, exploratory endpoint)? Accrual record of clinical trial group? Registration study? • What are the criteria to decide which COAs should be incorporated into a trial? • What are the advantages and challenges in incorporating single, composite or multiple COA measures in a clinical trial? Which approach? The Tiered approach with single major (composite) outcome: if positive then additional assessments can be evaluated vs. a multiple measures model that presents statistical challenges including issues with multiple comparisons. • What are the challenges in accrual and compliance? If included, should they always be mandatory? What is the definition of mandatory? Are there opportunities to improve compliance? Would electronic capture, interim analyses, penalties, reimbursement help improve compliance? • How should COA results be evaluated in the context of traditional outcomes (OS, PFS)?
Panel 4: • What are the clear priority action items (practical projects/tasks) to advance the field to improve and expand the use of COAs in brain tumor clinical trials for therapeutic agents seeking regulatory approval?

Summary of Panel Discussions:

Determining Brain Tumor Specific Signs, Symptoms, and Functions for Use in Clinical Outcome Assessments (Panel 1)

- The patient advocate indicated that, while it is obvious that patients wish to live longer, they also want to live “better” while they are alive. Therefore there is a need for more informed patient participation in medical care.
    - Up to 90 percent of patients are unable to return to work from the time of their diagnosis due to the symptoms of brain tumors.

- There is increasing recognition of the importance of evaluating the impact of therapy on patient-focused outcomes as a measure of clinical benefit.
    - Recent brain tumor clinical trials have demonstrated that symptom-based patient-reported outcome (PRO) measures are sensitive to tumor progression and differences in treatment arms, and may be related to overall survival (OS) and progression free survival (PFS).
    - Recent brain tumor clinical trials suggest that neurocognitive function may predict OS and PFS, as a decline in function often precedes imaging evidence of tumor progression.
- The relationships between symptoms, signs, and functions are complex, and there is a need to continue to analyze these relationships to determine what is being caused by the treatment and what is being caused by the tumor.
- Data from the Jumpstarting Brain Tumor Drug Development Coalition Patient and Caregiver Survey were presented and discussed.
- There is the need for a concise, prioritized list of symptoms, signs, and functions for which new COAs need to be developed. A set of COAs that could be more widely used as brain tumor COAs across trials would allow patients and doctors to make an educated decision about the course of treatment by comparing outcomes from therapies conducted in a standardized manner.
    - Across currently used brain tumor PRO instruments, there is great redundancy in symptoms included, the most common being headache and pain, the second being short-term memory; followed by expressive aphasia, or difficulty speaking; hemiparesis or hemiplegia (sometimes worded "weakness" on the instruments), and seizures.
    - There is inconsistent measurement of these common symptoms and signs across trials, and a wide variety of analyses used in the interpretation of the measurements. Multiple instruments utilize different measurement tools, and different questions are being asked to measure the same symptom. These inconsistencies make comparison of the measurements extremely difficult if not impossible, particularly from a quality of life (QoL) perspective, and provide little insight as to what impact the treatment in question will have on the patient.
- When determining a priority list for brain tumors, it is important to understand the disease process and natural history, and consider how patients present, and follow their trajectory.
    - The most common symptoms at the time of diagnosis are headache, weakness, speech and communication deficits, seizures, neurocognitive issues, and behavioral issues, as documented throughout the published literature.
    - The trajectory of individual patients can be varied. Some patients have symptoms that worsen over time while others have fixed deficits that do not change. Still other patients experience

symptoms that wax and wane in severity throughout the course of the disease.
    - Other medications, including corticosteroids, anticonvulsants, and chemotherapy can affect signs and symptoms.
- In developing COAs, it is important to consider both what is important to the patient as well as what is easily measurable and important within a clinical trial. It is also necessary to consider which of the signs or symptoms are sensitive to change, which cannot be improved upon, and which can be stabilized.
- Three general areas designated as priority areas to consider when developing COAs at the workshop include:
    1. Concomitant Medication Use
        - Presence/Absence at diagnosis
        - Dose
        - Duration
        - Changes in dose and duration
    2. Symptoms (PROs)
        - Headache/Pain
        - Seizures
        - Patient's perceived cognition
            i. Concentration
            ii. Memory
            iii. Executive Function
        - Aphasia (difficulty speaking)
        - Mood (depression/anxiety)
        - Paresis/Plegia (weakness)
    3. Functional Status (performance-outcome (PerfO), observer-reported outcome (ObsRO), clinician-reported (ClinRO), PRO)
        - Cognitive Function
        - Mobility/Walking
        - Basic activities of daily living (ADLs)
        - Instrumental ADLs
- When further prioritizing the above lists, there is a need to work toward the evaluation of the top 6 (or less) symptoms and functional measures, including neurocognition, for which there are existing assessments and instrumental ADLs, which need to be developed specifically for brain tumor clinical trials.
- The inclusion of patients in these types of discussions was stressed as important

Assessment of Patient Symptoms, Signs, Neurocognition, and Limitations in Functional Activities in Clinical Trials for Malignant Gliomas (Panel 2)

- Trials should be blinded when PROs or other COAs are being used.
- There is an understanding that there will be missing data, but if large gaps of data are present, the data cannot be relied upon. Electronic data

capture has been very successful in reducing missing data, and should be considered in future development of new COAs. Furthermore, patients and the clinicians in the trial must understand that COAs are important and a key endpoint, and that the collection of the data supporting these measures is critical to trial success.

- A major hurdle to the use of QoL as a regulatory endpoint is the difficulty in its measurement, as it is a term with a different meaning to everyone. Commonly used QoL measures include some domains that are of little relevance to drug development and domains that have little impact on patient outcomes. In light of these issues, there is a preference for the use of a symptom inventory instead of assessing QoL, as symptoms are more proximal to the disease and the treatment effect, and can often be measured more directly.
- A limitation in the use and understanding of current PRO measures included in brain tumor trials is that these instruments assess both the impact of the disease itself on the symptoms or signs as well as the effect of the treatment. There is debate about the need to separate these assessments.
- A COA that fits the following parameters is needed:
    - Ability to assess specific disease-related symptoms.
    - Has good psychometric properties.
    - Is feasible in the clinical trail context.
    - Has the ability to detect a well-defined, meaningful change in that patient population.
- There is a need for more targeted endpoint measures. While existing instruments may not be perfect, analysis of these measures may identify something suitable and useful for implementation now, while concurrently developing new instruments with better measurement properties.
- There is a need to use instruments that are specific to the brain tumor subpopulations being evaluated. Differences exist between patients with low-grade glioma, newly diagnosed-, first or second recurrence- high-grade glioma and brain metastasis. There could potentially be different types of scales at different phases.
- In high-grade glioma patients, it must be determined if the core symptoms all move in the same direction (i.e. unidirectional), which would potentially allow for a total symptom score. An alternative for symptoms that are highly variable across patients would be to have individual patients identify there is a most problematic symptom and assess this symptom and its progression or resolution with treatment as an endpoint.
- Adapting a currently available instrument for malignant glioma use is a possibility to begin using COAs in trials for these patients.
    - In terms of physical function, the European Organization for Research and Treatment of Cancer’s (EORTC) QLQ-C30's five-item physical functioning scale could potentially be used.
- The symptom, sign or function to be measured should determine the structure of the COA. For the symptom, sign or function to be measured, it

is important to first assess the quality of existing instruments, and their accuracy of measuring that construct prior to developing a new measure

- The most important aspects of an instrument are both content and construct validity, which determine if what is being measured is in fact what the instrument is purporting to assess and that the change detected is a real and accurate change in the target concept (e.g. physical function). This is required to correctly interpret results, and incorporate these results into the treatment labeling in a way that is accurate and not misleading to patients. The instrument should also be reliable and reproducible, and sensitive enough to detect clinically meaningful change.
    - We do not want to miss a treatment effect because an instrument does not perform reliably.
- There is much more work to be done with COAs in brain tumor clinical trials. No available measure is sufficient to address all the symptoms that were identified by Panel 1 as important. We need to look at the data we have from previous clinical studies and determine which symptoms, signs, and functions track with the disease, and what is the minimally, clinically important difference for these symptoms, signs and functions. One option in completing this task is to reanalyze available trial data to understand which existing COAs target the priority symptoms, signs and functions.
- It is essential to capture cognition and neurologic function, as they are the outputs of the organ in which the disease is occurring and the treatments are targeting.
    - The clinical trial battery represents that selection of cognitive tests and cognitive domains that are frequently problems for patients and that interfere with functional ADLs, particularly instrumental ADLs.
    - Neurologic Assessment in Neuro-Oncology (NANO) - an extension of the RANO effort - is an objective functional measure of neurologic capability that is meant to complement the objective measures of cognition, as well as subjective measures of QoL and patient symptoms.
- We need to consider whether it is best to perform a time to deterioration analysis versus a palliation or responder analysis. This represents a statistical challenge, and also a minimally important difference challenge that will have to be addressed.
- Moving forward, we need to determine how to 1) take the instruments we have now that are working and incorporate them into clinical trials; 2) improve on those existing instruments; and 3) plan/develop next generation instruments that would more accurately assess the priority symptoms.
    - Step 1 (also known as “low-hanging fruit”) - Incorporation of the symptom sub-scale of MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) and the Clinical Trial Battery for neurocognition into clinical trials whenever possible. There is the possibility of pre-specifying selected domains of interest and using

only these aspects of currently available COAs in trials, to avoid overburdening the investigators and thereby supporting improved compliance with collection of the data.
    - Step 2 - Refinement of current COAs along with a consolidation of symptom PROs into a single, universally used instrument. This can be guided by retrospective data analysis in which current instruments are mapped to priority domains (from Panel 1), and the best of the existing instruments are combined into a single measure.
    - Step 3 – Follow the development of new COAs such as the NANO, National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Brain Symptom Index (NFBrSI-24), and brain tumor specific EORTC instrumental ADL.

Creating Clinical Trial Designs that Incorporate Clinical Outcome Assessments (Panel 3)

- COAs provide an important dimension in evaluating outcomes in clinical trials. There is a need to collaborate and build consensus within the community to identify the best clinical trial designs incorporating COAs going forward.
- There is an opportunity to improve on the current process by educating patients and their families, as well as the clinical investigators on the importance of incorporating COAs in clinical trials.
- The same principles for incorporation of COAs into clinical trials that are used for other efficacy endpoints, including overall survival or progression free survival, can be applied. It is recommended that COA related endpoints be considered for use as, if not a co-primary efficacy endpoint, a key secondary efficacy endpoint in clinical trials so that the right resources are applied to capture the data consistently and systematically.
- If the patients on the experimental treatment maintained or improved their functional status based on the COA measure during an early, it was proposed that this should ultimately support advancement of the drug for patient care and product labeling.
- There is support for incorporation of COAs in early phase clinical trials prior to phase 3 so that previous experience and learning from using the measure(s) to test the intended hypothesis can be accrued to confirm treatment effects in later-phase registration trials.
- The COAs to be measured in a clinical trial should be clinically meaningful and have specificity for the symptom being measured, as well as feasibility of use with minimization of patient burden. Also, it needs to be presented in a language that the patient understands.
- The same COA instrument(s) should be used uniformly across trials. Standardization of analysis of COA data will also be necessary to ensure uniform interpretation across trials and trial centers.
- In identifying the COAs for use, there is a need to build on past

experience and learn retrospectively from COA data from previous trials.

- To inform the primary endpoint, it will be necessary to prospectively select a measure that is best going to represent the symptoms or the functional attributes of the patient population that are likely to respond to the therapeutic agent. The brain tumor patient population is heterogeneous, particularly as the disease progresses, so some measures may be more important than others at different stages of disease.
- Trial eligibility criteria can aid in ensuring treatment arms are well balanced with respect to use of instrument measures. It is possible that patients could be pre-specified into low- or high-symptom categories based on predefined criteria thresholds of severity.
- An overarching statistical challenge with the use of COAs in clinical trials is the potential for false positive claims, particularly with a multiple measures/comparisons model. Limiting the number of COAs to be evaluated and defining precisely the critical success factors, prospectively, can mitigate this potential issue. A tiered, sequential approach with a single major (composite) outcome, in which a finite list of concepts is measured, could be considered. If the primary COA were positive, additional analyses would be undertaken subsequently to examine other individual components.
- Resources and logistics required to implement the use of COA endpoints in a trial will need to be carefully considered. Some capital investment will be required to support training (and materials); as well as electronic data capture platforms. Missing data (particularly if the COA is an exploratory endpoint), and monitoring site compliance will need to be planned for. An interim feasibility assessment could be incorporated to ensure that the studies are being conducted appropriately before reaching the end of the trial.
- At the outset, sponsors and regulators should be clear about agreed upon PROs to assess efficacy, safety, and risk/benefit ratio in brain tumor trials. Early discussion between trial sponsors and the FDA is critical in ensuring success of these measures.

Creating an Action Plan (Panel 4)

- The panel stressed the importance of the need of more effective treatments, the need to keep open communication with the FDA both during trial development and instrument development (especially Study Endpoints and Labeling Development staff), and to involve patients in the development process.
- It was noted that if the COA and the trial are designed carefully, if the data are complete, and the drug has an impact on those particular symptoms or signs, success will follow.
- Action items that emerged from each panel review included:
    - Panel 1:

        - Prioritize symptoms to create a concise list, using patient-friendly language.
        - Consider endpoints in the context of concomitant medications.
        - Function needs to be measured from physical and cognitive perspectives.
    - Panel 2:
        - Identify the subsets within the currently available measures that are useful in assessing the symptoms prioritized by Panel 1.
        - Perform retrospective analysis of clinical trials that have utilized existing measures to confirm instrument accuracy.
        - Evaluate current measures and determine where enhancements can be made.
        - Improve data capture of COAs in clinical trial.
        - Evolve/Evaluate NANO, NFBrSI-24, and EORTC brain tumor specific instrumental ADL.
    - Panel 3:
        - Incorporate COAs into earlier trials.
        - Educate patients and investigators on importance of COAs in clinical trials.
        - Standardize implementation of tools and the analysis of the data.
        - Create statistical paradigms.
        - Develop assessments of patient's symptoms, physical functioning, and neurocognition and use in future brain tumor clinical trials whenever possible.
- Workshop participants created a list of next steps for moving the field forward:
    1. Review existing data sets for priority symptoms identified by Panel 1 and use this review to further refine the priority symptom list.
    2. Work with the FDA's SEALD team to map existing measures to determine which measures address specific symptoms.
    3. Perform retrospective analysis and determine:
        - Most consistent symptoms.
        - Most consistent measures of those symptoms.
        - Minimal improvement required.
        - Patient population.
    4. Educate sponsors, investigators, and patients on the importance of COAs in brain tumor clinical trials.
    5. Create a coalition to develop a consensus series of clinical trial designs for implementation in multi-site trials in which COAs are used.

Conclusion:
The workshop produced a number of suggested action items intended to represent a starting point for future work in the area of COA use in brain tumor clinical trials. The Jumpstarting Brain Tumor Drug Development Coalition is

committed to forming a planning group to discuss the consensus points and create a strategy to advance this initiative, in coordination with the outcomes of the first endpoints workshop on imaging.

Although malignant glioma patients are stricken with a number of symptoms, it was agreed upon that identification of a modest list of disease-related symptoms are needed. In order to reach this goal, a working group needs to be formed in which consensus can be made on the priority symptoms, as well as the tool(s) for measuring these symptoms. Ideally, this group will utilize existing clinical trial data and existing (MDASI) and emerging (NFBrSI-24) tools and work towards the development of a symptom PRO measure in which the items correspond to the other concepts of interest being measured in the trial.

There is no standard physical functioning test for use in malignant glioma trials. Therefore, it was discussed that a COA (PerfO, ClinRO and/or PRO) be developed either by building on components of existing tools (EORTC QLQ-C30) from other cancers and diseases, or creating a new, well-defined, and reliable assessment.

Prior consensus among neuropsychologists has led to the Clinical Trial Battery, a PerfO, being the standard neurocognitive test used in brain tumor clinical trials. However, there is a need to address and develop standards for how and when the test is administered, as well as how the results are analyzed and interpreted.

The importance of capturing COAs in brain tumor clinical trials must be relayed and emphasized to all stakeholders to help foster support for the inclusion of these measures. The Jumpstarting Brain Tumor Drug Development Coalition could lead an educational effort to demonstrate that innovation, adaptation, and investment in COAs by academia, pharmaceutical companies, governmental agencies, and patient advocates is needed to move the community closer to more and better treatments.

The brain tumor endpoints workshop focusing on COAs was very successful in that it provided the patient perspective in regards to treatments, enabled open discussions around alternative endpoints, and developed an action plan that has the potential to increase the inclusion of these alternative endpoints in future brain tumor clinical trials. In this context, we anticipate that these changes will create an environment that is more conducive to the expansion of the scope of research by enhancing the investment in brain tumor treatments, and ultimately deliver a pipeline of novel agents and treatment strategies to this patient population.

To learn more about the outcomes of the workshop and the overall brain tumor clinical trial endpoints initiative, please contact David Arons at darons@braintumor.org, or Jennifer Helfer, PhD at jhelfer@braintumor.org.