Reply to Trout et al: Clinical trials: A plea to cooperative groups, consortia, pharmaceutical companies, and lead investigators for reasonable imaging protocols

Nicholas Gottardo[1], Maryam Fouladi[2], and Dennis Shaw[3]

[1]Princess Margaret Hospital for Children
[2]Nationwide Children's Hospital
[3]Seattle Children's Hospital

June 7, 2023

Reply to: Clinical trials: A plea to cooperative groups, consortia, pharmaceutical companies, and lead investigators for reasonable imaging protocols

Nicholas Gottardo, MD[1], Maryam Fouladi, MD,[2] Dennis Shaw, MD[3]

[1] Telethon Kids Cancer Centre, University of Western Australia, Perth, Australia

[2] Division of Hematology, Oncology, and Bone Marrow Transplant, Nationwide Children's Hospital, Columbus OH

[3] Department of Radiology, Seattle Children's Hospital, Seattle, WA

*Correspondence to:

Dennis Shaw, MD, Seattle Children's Hospital, Department of Radiology M/S MA. 7.220

4800 Sand Point Way NE, Mail Stop MA. 7. 220, Seattle WA 98105

Tel: 206 987 2134

Email: Dennis.shaw@seattlechildrens.org

Abstract : none

Text Word count : 1030

Brief Running Title : Reply to Trout et al

Key words: imaging, pediatric cancer, clinical trials, CNS

Figures/tables: 0

Abbreviations

COG	Children's Oncology Group
RAPNO	Response Assessment in Neuro-Oncology
CNS	Central nervous system

Remarkable progress has been made in the treatment of childhood cancer over the last half century with

overall survival rising from only 4% to over 80%.[1] These improvements can be largely attributed to the conduct of sequential clinical trials by international cooperative groups over decades through an iterative process that builds on successive trials. Another important result of the high participation rate in pediatric cancer cooperative group clinical trials has been standardization of treatment internationally. This standardization itself can also be credited with improvements in outcomes for children with cancer.[1] However, not all childhood cancers have experienced equal improvements, with many brain tumors continuing to have poor outcomes.[1]

In the May 2023 issue of *Pediatric Blood and Cancer* , Trout el al[2] make an appropriate plea for required imaging in cooperative clinical trials to be as minimally burdensome as possible both to clinical imagers and patients. The authors outline a rational set of points to follow in setting imaging requirements including developing, with multidisciplinary input, guidelines that are widely accepted, accessible and easily implemented, and not altering these standards unnecessarily.

Ultimately, this involves a balance between allowing use of local imaging protocols with as wide a latitude as possible and staying within standardly available imaging capabilities, while still providing comprehensive data needed for accurate staging and response assessments on prospective multi-institutional clinical trials.

Imaging, as noted by Trout et al,[1] is a surrogate for treatment response. We would also emphasize that imaging is integral to accurate disease *staging* at diagnosis and throughout therapy. Improving the accuracy of disease staging is critical to improving patient outcomes since incorrect staging, in and of itself, can result in under or over treatment, leading to poorer survival or unnecessary acute and long-term treatment-related sequelae, respectively.

Problematic imaging has previously been reported in retrospective central imaging reviews.[3,4] In the*retrospective,* centralized review of initial staging neuroimaging in the Children's Oncology Group (COG) A9961 trial in standard-risk medulloblastoma, 7% (30/421) of patients were deemed ineligible due to the presence of residual (n=15) or metastatic disease (n=15) and over 10% had inevaluable neuroimaging studies. Both groups had significantly poorer survival than those with centrally-confirmed standard-risk disease.[3] Despite the report of this finding, recently reported results of the successor study, COG ACNS0331, show a similar incidence of inevaluable or ineligible staging neuroimaging studies on retrospective review.[4]

This issue has become increasingly concerning and critical to address prospectively given the greater tailoring of treatment in trials based on this staging. For instance, in patients with favorable-risk disease features and excellent survival outcomes, such as WNT medulloblastoma (NCT02724579) or CNS germ cell tumor (NCT04684368), current COG trials are evaluating treatment-reduction strategies to mitigate acute and long-term treatment-related sequelae. In such studies, insufficient/inadequate imaging may adversely impact therapy decisions for an individual patient who is mis-staged at a) diagnosis and is undertreated, or b) critical points in treatment (e.g. post induction chemotherapy) where incorrect response assessment and/or restaging would potentially result in inappropriate therapy decisions. In addition to detrimental effects on individual patients, which may occur regardless of whether a patient is treated on a therapeutic trial, inadequate imaging can also compromise the integrity of the trial as enrollment of ineligible or inevaluable patients or their assignment to inappropriate therapeutic arms in multi-institutional trials that span years may impact the results of potentially practice-changing trials.

To avoid over or undertreatment of patients, optimized and sufficient imaging for accurate staging is critical. Determining imaging requirements in COG clinical trials involves collaboration among radiologists, oncologists and radiation oncologists. The goal is to ensure imaging requirements provide adequate information to accurately guide treatment and evaluate response while remaining within well-established national/international imaging guidelines such as the Response Assessment in Neuro-Oncology (RAPNO). Typically, imaging modality, timing, anatomic coverage and need for contrast are determined using such established imaging guidelines which are generally adopted as standard-of-care. However, allowing "standard-of-care" imaging to be entirely defined locally can prove problematic where sites have not adopted such established imaging guidelines for sufficient staging and response assessments in their routine clinical proto-

cols. The requirement for adequate routine clinical imaging for staging is distinct from imaging for research and correlative studies that consortia with appropriate mandates, site expertise and funding can consider as secondary or exploratory objectives and may warrant site funding.

Recognizing the breadth of the over 220 COG participating institutions and following the principles advocated by Trout et al,[2] the COG Imaging Discipline is publishing a series of white papers on pediatric cancer imaging, to promulgate standards of care for tumor imaging. Notably, these MRI parameters have been designed for implementation in routine clinical practice, as well as multi-center clinical trials,[5] and supported by conclusive data from generations of studies over decades.[3,4,6]Moreover, in response to concerns about inadequate imaging and/or misinterpretation, recent COG brain tumor trials have adopted a rapid central imaging review with optimized MRI sequences.[5]The early experience of centralized imaging on the COG ACNS1422 study for average-risk WNT medulloblastoma patients (NCT02724579), was consistent with previous reports that approximately 10% of patients are wrongly staged by imaging locally.[7] This improved quality control, alone, affords the opportunity to improve survival in a subgroup of patients even without any new therapeutic interventions.

Furthermore, understanding the burden of requiring imaging that may vary from a site's routine and requesting repeat imaging of subjects to ensure adequate staging, the COG has recently undertaken a proactive survey of COG site MR brain tumor imaging protocols. Response to date reveals variable alignment of local institutional imaging with international, published standards. By providing individual site feedback, we hope to make the prospective adoption of well-established imaging guidelines more efficient. Ultimately, this approach will lead to improved staging and treatment decision making for children with brain tumors regardless of whether they are treated on clinical trials.

In summary, we agree with the plea by Trout et al for cooperative clinical trial imaging to be reasonable and minimally burdensome. The conduct of clinical trials is becoming increasingly complex, often requiring real-time assessment of imaging by central reviewers. We, who conduct these cooperative trials, are dependent on, and appreciative of, local site efforts required to maintain imaging necessary to support these advances in treatment of pediatric tumors.

References

1. Adamson P.C. Improving the outcome for children with cancer: Development of targeted new agents. *CA Cancer J Clin* . 2015;65(3): 212-20.
2. Trout AT, Norris RE, de Blank PMK, Backus LR, Towbin AJ, Nash JM. Clinical trials: A plea to cooperative groups, consortia, pharmaceutical companies, and lead investigators for reasonable imaging protocols. *Pediatr Blood Cancer* . 2023;e30362.
3. Packer R.J., Gajjar A., Vezina G., et al: Phase III Study of Craniospinal Radiation Therapy Followed by Adjuvant Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma. *J Clin Oncol.*(2006); (24): 4202-4208
4. Michalski JM, Janss AJ, Vezina LG, et al. Children's Oncology Group Phase III Trial of Reduced-Dose and Reduced-Volume Radiotherapy with Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma. *J Clin Oncol* . (2021); 39(24), 2685-269
5. Jaju A, Li Y, Dahmoush H, et al. Imaging of pediatric brain tumors: A COG Diagnostic Imaging Committee/SPR Oncology Committee/ASPNR White Paper. *Pediatr Blood Cancer* . 2023;70(Suppl. 4):e30147.
6. Leary SES, Packer RJ, Li Y, et al: Efficacy of Carboplatin and Isotretinoin in Children With High-risk Medulloblastoma: A Randomized Clinical Trial From the Children's Oncology Group. *JAMA Oncol.*2021;7(9):1313-1321.
7. Gottardo N.G., Leary S., Kang G., Gossett J., et al. (2020). How to increase survival in 7 to 10% of patients with average-risk medulloblastoma without new therapies: early prospective neuroradiology screening experience from the Children's Oncology Group.*Neuro-Oncology.* (Supplement_3):*Neuro Oncol.* 22(Suppl 3): iii396