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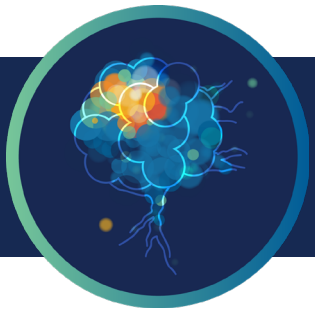
EXPERT INSIGHTS: BRAIN METASTASIS IN CLINICAL TRIALS, FEATURING NEURO-ONCOLOGY EXPERT, DR. MARIKO DEWIRE-SCHOTTMILLER



Written in collaboration with Jia You, PhD, Clinical Trial Manager, Jessica Schreiber, Clinical Research Associate, and Erica Horn, Clinical Research Associate at Medpace.

Dr. Mariko DeWire-Schottmiller is a distinguished, board-certified Pediatric Hematologist and Oncologist with over a decade of experience in clinical research, academia, and clinical oncology practice, specializing in Oncology and Neuro-oncology.

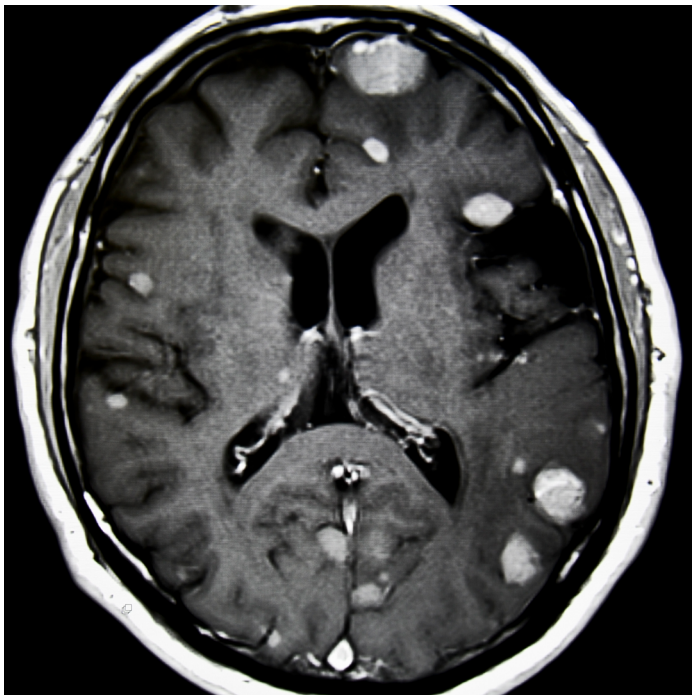
Dr. DeWire-Schottmiller held leadership roles in organizations, including The International DIPG/DMG Registry, Pediatric Brain Tumor Consortium, and Children's Oncology Group. She is an active member of ASCO, SNO, and AACR. Furthermore, Dr. DeWire-Schottmiller has contributed significantly to academia, having served as an Associate Professor at the University of Cincinnati, College of Medicine, Cancer and Blood Diseases Institute, at Cincinnati Children's Hospital. As a Principal Investigator in the field of oncology, she has authored several peer-reviewed articles and journals in the field of oncology; her expertise is highly regarded in the fields of oncology and neuro-oncology.

Share insight into your background in oncology and neuro-oncology, in addition to your involvement in clinical development.

Upon entering medical school, I found my calling in Pediatric Medicine. It was during an elective rotation in Hematology and Oncology that I developed a clinical interest in Pediatric Hematology and Oncology. My undergraduate studies, which included Medical Technology with an emphasis in Hematology and Oncology, further fueled my passion. As I cared for pediatric patients with these conditions, I became determined to pursue a robust Pediatric Hematology and Oncology program. During my training and fellowship, I was fortunate to have exceptional mentors in Pediatric Neuro-Oncology and clinical trial development, which laid the foundation for my career as a Pediatric Neuro-Oncologist. My goal has always been to contribute to improved outcomes and higher quality of life for these patients. My dedication to clinical trial development was solidified during my fellowship, where I witnessed varying responses to supposedly cutting-edge therapies in patients with the same diagnosis.

The majority of my academic career was spent at the Cancer and Blood Disease Institute at Cincinnati Children's Hospital Medical Center (with a large national referral base). My clinical expertise covered primarily solid tumors with a keen focus on aggressive CNS tumors in children and young adults, including Diffuse Intrinsic Pontine Glioma (DIPG) and high-grade gliomas refractory to current therapies. I was honored to care for these patients, translating their hopes into meaningful research and clinical trial development to improve the outcome of pediatric brain tumors, in addition to maximizing their quality of life.

During my time in clinical practice, particularly in pediatric neuro-oncology, the limited trial options were a significant challenge due to the scarcity of tumor tissue for studying the biology of the disease, as pediatric and adult CNS tumors may exhibit different biology. Early-phase I studies excluded primary CNS tumors, which has implications for both pediatric and adult oncology trial options. Today, I am dedicated to the current phase of my career, contributing to therapeutic advancements in primary CNS tumors and improving trial access for patients with metastatic CNS disease, by supporting Sponsors in innovative trial development.



What are some challenges, considerations, and risks involved in conducting clinical trial research in neuro-oncology, specifically for patients with treated or active brain metastasis?

Patients with brain metastasis are a heterogeneous population, each with their unique primary disease and prior treatments. Furthermore, there is difficulty in defining a suitable primary endpoint in this patient population. There are uncertainties about including patients with brain metastasis in clinical trials, and mitigation is to consider a separate subgroup within the trial as this will inform the development of eligibility criteria in later phases, and this is supported by the FDA (Guidance: Evaluating Cancer Drugs in Patients with Central Nervous System Metastases 2021 and Cancer Clinical Trial Eligibility Criteria: Brain Metastases 2020).

Further considerations include stratification according to types of metastases: stable or treated, active brain metastases, and leptomeningeal disease (LMD), with eligibility requirements for each type. Pending the patient's symptoms, concomitant medications for management, including steroids, antiepileptic drugs, analgesics, and other supportive medications are specific to this patient population and imperative in providing drug-drug interactions and impact on the pharmacokinetics of study product in early drug development. Adverse events, SAEs, and DLTs need to be clarified in the protocol for this population given the prior therapies for the CNS disease. An example is reporting adverse events related to study treatment versus prior radiation therapy versus disease.

What are some of the unique challenges faced when conducting neuro-oncology trials?

One of the hurdles is to obtain efficacy endpoints. For example, commonly used disease evaluations are RANO-BM (brain metastasis) and RECISIT 1.1. These response methodologies include the definition of response according to RANO-BM while also addressing the systemic disease with RECIST 1.1. Metastatic cancer, including brain metastases, is a systemic disease; thus, efficacy is demonstrated at all disease sites and not isolated to the brain metastases. Utilizing RECIST and RANO-BM as endpoints may result in variations across institutions as there may be a reviewer focused on RECIST and a different reviewer focused on RANO requiring an additional logistic at the site level. Additionally, there is a potential for a different selection of CNS lesions in RECIST vs. RANO by the individual radiologist, and this may result in a different responses. Furthermore, some institutions may have internal guidance to not include a brain lesion as a target lesion for RECIST 1.1 response review. Addressing these challenges will include inquiring about the site's process during the feasibility evaluations. This is where a highly experience CRO can have great utility and determine how each site determines response.

Data entry into EDC needs to be aligned regarding CNS target lesions in RECIST at baseline and RANO-BM at baseline, in addition to processes for the development of new lesions, thus, clear eCRF guidelines and considerations for CRA training are imperative. RANO-BM differs from RECIST in that the CNS is the primary organ for target and non-target lesions, and steroid use, in addition to clinical deterioration, contributes to the overall response. Furthermore, RANO-BM is applicable to clinical care (radiographic progression versus clinical progression); whereas RECIST 1.1 is solely based on imaging measurements.

Study endpoints regarding efficacy for brain metastases must be clearly delineated in the protocol. Overall survival can be challenging to attribute death due to CNS disease. Objective Response Rate (ORR) and

Progression-Free Survival (PFS) must be determined based on evaluations in all of the metastatic diseases, regardless of CNS or extra-CNS disease. CNS activity may be considered as a secondary endpoint.

Multidisciplinary collaboration is key, including investigators, the site's research team, and a CRO that can provide additional medical and operational support, in addition to collaborative and readily available support from data management.

How have recent breakthroughs in targeted therapies offered new hope for patients, specifically those with brain metastasis?

Precision medicine, immunotherapies, Stereotactic Radiosurgery (SRS), and radiopharmaceuticals have resulted in durable responses resulting in support in including these patients in early drug development. Furthermore, the agency has provided guidance to encourage patients with CNS metastasis in early drug development. Given this guidance, I anticipate more studies will support the enrollment of patients with brain metastases. Having cared for patients with primary CNS tumors and enrolled in clinical trials, these patients do benefit from clinical trials. Brain metastases are the most common CNS tumor in adults, and I am hopeful these patients will be considered for more studies.

What motivates you and your interest in clinical research – particularly in oncology research?

As a pediatric neuro-oncologist who is now working in a CRO, my motivation stems from the commitment to support moving clinical trials into the clinic and expanding access to patients with CNS tumors, including adults, adolescents, and children. Every patient I have cared for, enrolled on a clinical trial, or informed that a trial was not available for them continues to remain in my memory and fuels my commitment to do my best in supporting the advancement of the field as I participate in collaboration with Sponsors in drug development and translating into novel clinical trials in patients with CNS tumors including CNS metastases and primary CNS tumors.

Why should Sponsor's consider a partnership with an Oncology CRO like Medpace?

Oncology is our largest therapeutic area integrated with sub-specialties within Oncology. Hematological malignancies, solid tumors, CNS tumors, and metastatic advanced disease will have different requirements given the complex variations within these areas. Our Oncology team at Medpace have therapeutic expertise in the different sub-specialty areas clinically, academically, and within the industry. We take responsibility in knowing the most up to date guidance in supporting the clinical development of programs and are keen in sharing our knowledge and lessons learned in a partnership with our Sponsors with the common goal to improve the outcome of cancer patients.

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Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical, and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system , and anti-viral and anti-infective.