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Guidance for Sponsors
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# Neurological Imaging: Contrast Enhancement in Clinical Trials

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**Intravenous contrast enhancement is one of the most informative signals in neurological imaging. Where the blood-brain barrier is intact, gadolinium stays in the vessels and the brain does not enhance; where disease has disrupted it, in tumors, active demyelination, infection or inflammation, contrast leaks into tissue and lights up the lesion. That simple principle underlies the primary endpoints of trials in glioma, multiple sclerosis and many other CNS conditions. The past decade has also brought a new understanding of gadolinium retention, a shift to macrocyclic agents, and the approval of high-relaxivity agents that work at a fraction of the traditional dose. This issue reviews the physiology, the patterns and the practical choices sponsors now face.**

## How Gadolinium Contrast Works

Gadolinium is a paramagnetic metal that shortens the T1 relaxation time of nearby water protons, making tissue that contains it appear bright on T1-weighted images. Because free gadolinium is toxic, it is administered bound to a chelating ligand, either linear or macrocyclic in structure. The standard dose for most agents has been 0.1 mmol per kilogram of body weight. Enhancement occurs wherever the agent accumulates: in vessels, in tissues that lack a blood-brain barrier such as the pituitary, choroid plexus and dura, and in any lesion where the barrier is broken.

Enhancement patterns carry diagnostic meaning. Ring enhancement with central necrosis suggests high-grade glioma, metastasis or abscess; open-ring or incomplete-ring enhancement favors demyelination; leptomeningeal enhancement suggests meningitis or carcinomatosis; and dural enhancement points to pachymeningeal processes. The classic review of these patterns by Smirniotopoulos and colleagues remains a foundational reference for neuroradiologists.[1]

## Enhancement as a Trial Endpoint

In multiple sclerosis, the number of new gadolinium-enhancing T1 lesions was for years the primary endpoint of Phase 2 trials, because each enhancing lesion marks acute inflammation and lesions accrue far faster than clinical relapses. In glioma, the enhancing tumor is what RANO and RANO 2.0 measure, and the 2023 update of those criteria made the post-radiotherapy MRI the baseline and required confirmation of progression to separate true growth from treatment-related enhancement.[2] The standardized Brain Tumor Imaging Protocol specifies matched pre- and post-contrast 3D T1-weighted acquisitions precisely so that enhancement can be compared reliably over time.[3]

What makes enhancement a good endpoint, its sensitivity to barrier disruption, also makes it vulnerable to confounding. Corticosteroids reduce enhancement by sealing the barrier; antiangiogenic drugs such as bevacizumab do the same and can produce apparent response without true tumor shrinkage; and radiation can increase enhancement in the absence of tumor growth. Protocols must therefore fix the timing of imaging relative to steroid dosing, specify the delay between injection and acquisition, and read enhancement alongside T2 and FLAIR signal.

## Gadolinium Retention and the Shift to Macrocyclic Agents

In 2014, Kanda and colleagues reported that signal in the dentate nucleus and globus pallidus increased with cumu-

lative doses of gadolinium in patients with normal renal function, and McDonald and colleagues subsequently confirmed gadolinium deposits in post-mortem brain tissue.[4,5] Retention is greatest with linear agents and lowest with macrocyclic agents. In December 2017 the FDA required a new class warning and medication guide for all gadolinium-based contrast agents, and the European Medicines Agency suspended most linear agents for intravenous use.[6] No harm has been established from brain retention, but the practical result has been a near-universal move to macrocyclic agents in trials, where participants may receive many doses.

The older safety concern, nephrogenic systemic fibrosis in patients with severe renal impairment, has essentially disappeared with the use of the agents the American College of Radiology classifies as Group II, for which the risk is so low that renal function screening is considered optional.[7]

## New Agents, Lower Doses

Two high-relaxivity macrocyclic agents now allow equivalent enhancement at reduced gadolinium dose. Gadopiclenol was approved in September 2022 for CNS and body imaging at 0.05 mmol/kg, half the conventional dose.[8] Gadoquatrane, a tetrameric macrocyclic agent, was approved in June 2026 at 0.04 mmol/kg, a 60 percent reduction.[9] Deep-learning methods that reconstruct full-dose-quality images from low-dose acquisitions are also under study. For trials, a switch of agent or dose mid-study is a protocol change that affects endpoint comparability, so the agent, dose and injection protocol should be fixed in the imaging charter before enrollment and any change assessed with a bridging analysis.

## Guidance for Sponsors

### Contrast-enhanced MRI in CNS trials

- **Fix the agent and dose.** Specify a single macrocyclic agent, dose in mmol/kg and injection rate for the entire trial.[6,7]
- **Match acquisitions.** Identical pre- and post-contrast 3D T1 sequences with a defined post-injection delay.[3]
- **Control the confounders.** Record steroid and antiangiogenic exposure and schedule imaging consistently relative to dosing.[2]
- **Interpret enhancement in context.** Read with T2/FLAIR and, where relevant, perfusion to separate tumor from treatment effect.[2]
- **Document safety screening.** Follow ACR Group II guidance and capture every administration for cumulative dose tracking.[7]
- **Read centrally.** Blinded neuroradiologists using standardized criteria and adjudication.[10]

## Summary

Contrast enhancement remains the clearest window into blood-brain barrier disruption, and therefore into the activity of CNS disease. Understanding what it shows, what can mimic or suppress it, and how the agents themselves have changed lets sponsors design protocols in which enhancement is a robust, reproducible endpoint rather than a source of noise.

## About the Author

Dr. Greg Boys, Medical Director of Neurological Imaging at Intrinsic Imaging, wrote the original edition of this issue. He completed his residency in diagnostic radiology and fellowship training in neuroradiology, and he leads the design and central reading of CNS imaging endpoints across neuro-oncology, neurodegenerative and demyelinating disease trials. He is board-certified in diagnostic radiology.

## References

1. Smirniotopoulos JG, Murphy FM, Rushing EJ, Rees JH, Schroeder JW. Patterns of contrast enhancement in the brain and meninges. *RadioGraphics.* 2007;27(2):525–551. doi.org/10.1148/rg.272065155

2. Wen PY, van den Bent M, Youssef G, et al. RANO 2.0: update to the Response Assessment in Neuro-Oncology criteria for high- and low-grade gliomas in adults. *J Clin Oncol.* 2023;41(33):5187–5199. pubmed.ncbi.nlm.nih.gov/37774317

3. Ellingson BM, Bendszus M, Boxerman J, et al. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. *Neuro Oncol.* 2015;17(9):1188–1198. doi.org/10.1093/neuonc/nov095

4. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology.* 2014;270(3):834–841. doi.org/10.1148/radiol.13131669

5. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology.* 2015;275(3):772–782. doi.org/10.1148/radiol.15150025

6. U.S. FDA. Update on FDA approach to safety issue of gadolinium retention after administration of gadolinium-based contrast agents. 2018. fda.gov

7. American College of Radiology Committee on Drugs and Contrast Media. ACR Manual on Contrast Media. acr.org

8. U.S. FDA. Drug Trials Snapshots: Elucirem (gadopiclenol). September 2022. fda.gov

9. Bayer. FDA approves Ambelvist (gadoquatrane) injection for contrast-enhanced MRI. June 2026. bayer.com

10. U.S. FDA. Clinical trial imaging endpoint process standards: guidance for industry. April 2018. fda.gov

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