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Guidance for Sponsors
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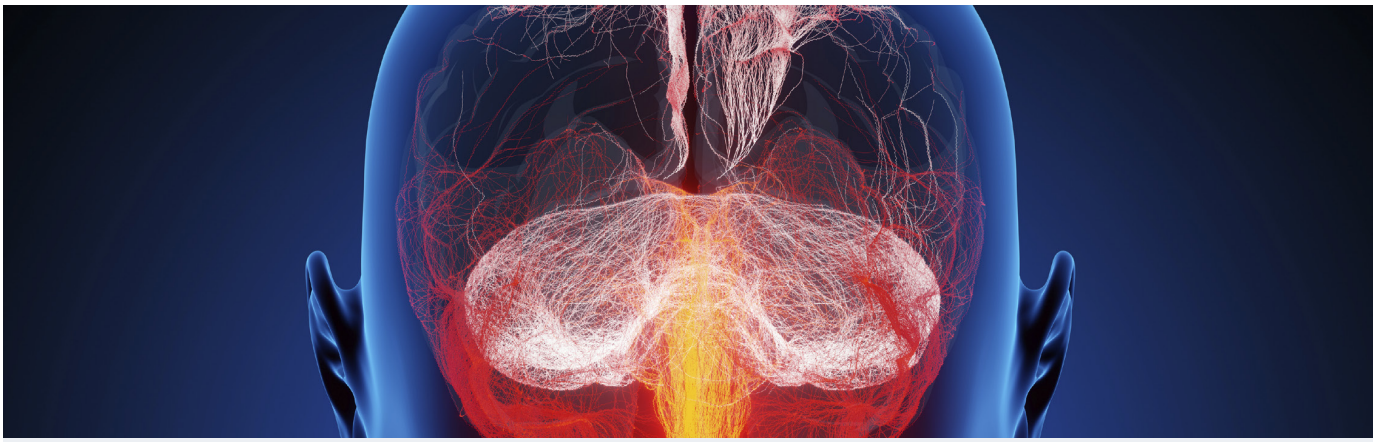
Traumatic Brain Injury: Medical Imaging in Clinical Trials

By David Wood, M.D., Diagnostic Radiology and Neuroradiology · Updated for 2026 by Intrinsic Imaging



Traumatic brain injury (TBI) caused about 69,000 deaths in the United States in 2021 and more than 214,000 hospitalizations in 2020, and an estimated 69 million people worldwide sustain a TBI each year.[1,2] Despite decades of effort, no neuroprotective drug has succeeded in a Phase 3 trial, and the heterogeneity of the injury is a leading explanation. Imaging is central to solving that problem. CT remains the first-line tool, MRI reveals injury CT cannot see, blood biomarkers now help decide who needs a scan, and a new classification framework published in 2025 makes imaging a formal pillar of how TBI is characterized. This issue reviews what sponsors need to know.

Why TBI Trials Have Been So Difficult

TBI ranges from a brief concussion to a devastating polytrauma, and the Glasgow Coma Scale that has defined 'mild,' 'moderate' and 'severe' since 1974 captures only a fraction of that variability. Two patients with identical GCS scores may have entirely different intracranial pathology, prognoses and responses to therapy. Trials that enroll on GCS alone mix populations that cannot be expected to respond uniformly to any single intervention.

In 2025 an NIH-NINDS-sponsored international initiative proposed a new characterization framework, CBI-M, built on four pillars: Clinical presentation, Biomarkers (blood-based), Imaging, and Modifiers such as age, comorbidities and injury mechanism.[3] For the first time, imaging findings are an explicit component of how TBI is classified, and trial sponsors are expected to describe their populations accordingly.

CT: Still First, but Now Structured

Non-contrast CT remains the primary acute imaging test because it is fast, universally available and detects the surgical emergencies that matter most: epidural and subdural hematoma, contusion with mass effect, and midline shift. For trials, however, a free-text CT report is not enough. Structured scoring systems convert CT findings into reproducible prognostic categories. The Marshall classification, developed from the Traumatic Coma Data Bank, groups injuries by the presence of mass lesions, cisternal compression and midline shift.[4] The Rotterdam score refined it by adding epidural hematoma and traumatic subarachnoid or intraventricular hemorrhage, improving outcome prediction.[5]

The American College of Radiology and American Society of Neuroradiology published evidence-based recommendations for conventional neuroimaging in TBI that remain the standard reference for which patients should be imaged, when and how.[6] The NINDS Common Data Elements define a standard vocabulary for recording CT and MRI features so that findings are comparable across trials and sites.[7]

MRI Sees What CT Misses

Many patients with normal CT scans have abnormal brains. In the TRACK-TBI pilot, 27 percent of patients with mild TBI and a normal CT had abnormalities on early MRI, and the presence of brain contusion or four or more foci of hemorrhagic axonal injury predicted worse three-month outcomes.[8] Susceptibility-weighted imaging detects microhemorrhages that mark diffuse axonal injury; FLAIR identifies non-hemorrhagic shear injury and edema; and diffusion tensor imaging quantifies white-matter integrity through fractional anisotropy. Advanced techniques including perfusion, spectroscopy and functional MRI remain research tools, but the ACR-ASNR evidence re-

view supports their use as exploratory trial endpoints when protocols are standardized.[9]

Blood Biomarkers and Imaging Together

The FDA authorized the first blood test for concussion evaluation in 2018, measuring glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1) to predict which patients with mild TBI will have intracranial lesions on CT. In 2024 a whole-blood version was cleared for use at the bedside on a point-of-care analyzer, returning results in about 15 minutes.[10] These assays reduce unnecessary CT scans in the emergency department and, in trials, offer an objective screening tool that complements imaging rather than replacing it. CBI-M explicitly pairs blood biomarkers with imaging as the two biological pillars of classification.[3]

Imaging Endpoints for TBI Trials

Imaging in TBI trials serves three roles. First, as an enrollment criterion: a protocol may require a specific CT pattern, such as traumatic subarachnoid hemorrhage, or a lesion volume above a threshold. Second, as a mechanistic endpoint: change in contusion or edema volume, hematoma expansion, or longitudinal change in DTI metrics. Third, as a safety measure: new or enlarging hemorrhage in trials of anticoagulant reversal or antithrombotic therapy. In each role, consistency is the challenge. Scanner differences, slice thickness, timing from injury and reader variability can each swamp a treatment effect. A central imaging core lab with a defined acquisition protocol, trained readers and adjudication is the standard solution.

Guidance for Sponsors

Imaging a TBI trial

- **Characterize, do not just grade.** Describe the population using CT and MRI findings alongside GCS, consistent with the CBI-M framework.[3]
- **Use a structured CT score.** Apply Marshall or Rotterdam scoring centrally at baseline for stratification.[4,5]
- **Add MRI where the question demands it.** SWI, FLAIR and DTI reveal injury that CT cannot, particularly in mild TBI.[8,9]
- **Adopt the NINDS Common Data Elements.** Standardize imaging variable definitions across sites.[7]
- **Consider blood biomarkers for screening.** GFAP and UCH-L1 can rationalize who is scanned.[10]
- **Read centrally and blind.** Use independent neuroradiologists with adjudication to control reader variability.[11]

Summary

TBI is not one disease, and trials that treat it as one have failed. With structured CT scoring, MRI that reveals hidden injury, point-of-care blood tests and a classification framework that finally makes imaging a defining pillar, sponsors now have the means to enroll the right patients and measure what their therapies actually do.

About the Author

Dr. David Wood, a radiologist at Intrinsic Imaging, wrote the original edition of this issue. He completed his residency in diagnostic radiology and fellowship training in neuroradiology, and he interprets CT and MRI of the brain and spine across trauma, vascular, oncologic and degenerative disease. He is board-certified in diagnostic radiology.

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Contact

Intrinsic Imaging, LLC
580 Main Street, Suite 210
Bolton, MA 01740
Tel: +1 978-616-4650
Contact@IntrinsicImaging.com
www.IntrinsicImaging.com