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Guidance for Sponsors
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Tissue Iron Deposition: MRI Quantitation in Clinical Trials

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Iron overload is the inevitable consequence of chronic transfusion and of ineffective erythropoiesis in thalassemia, sickle cell disease and myelodysplastic syndromes. Each unit of blood delivers about 200 mg of iron the body cannot excrete, and the resulting deposition in liver, heart and endocrine organs was for decades the leading cause of death in transfusion-dependent thalassemia. MRI changed that. Non-invasive measurement of liver iron concentration and cardiac T2* replaced biopsy, revealed cardiac iron that serum ferritin could not predict and gave chelation trials objective endpoints. With gene therapies and new disease-modifying drugs now approved, quantitative iron MRI is more important than ever. This issue explains the methods and what sponsors should specify.

Why Ferritin and Biopsy Were Not Enough

Serum ferritin is inexpensive and widely used but is an acute-phase reactant that rises with inflammation and infection, and it correlates poorly with cardiac iron. Liver biopsy measures iron directly but is invasive, prone to sampling error from heterogeneous deposition and fibrosis, and unsuitable for repeated measurement in a trial. Neither method could identify the patients whose hearts were loading iron while their ferritin and liver values looked acceptable.

MRI exploits the fact that iron is paramagnetic. Tissue iron shortens the transverse relaxation times T2 and T2*, and the corresponding relaxation rates R2 (1/T2) and R2* (1/T2*) increase in proportion to iron concentration. Measuring those rates provides a quantitative, reproducible and non-invasive estimate of tissue iron.

Liver Iron Concentration

Two MRI methods have been calibrated against biopsy. The spin-echo R2 method, commercialized as FerriScan, was validated against biopsy liver iron concentration and cleared by the FDA in 2005; it requires centralized analysis and is the method most often used in chelator registration trials. The gradient-echo R2* method is faster, acquired in a single breath-hold, and was calibrated against biopsy by Wood and colleagues in 2005, with subsequent work establishing that R2* calibration is consistent across scanners and field strengths when acquisition parameters are controlled.[1,2] Recent validation studies confirm close agreement between R2* and R2-based LIC when standardized protocols are used.[3]

Clinically, LIC below 3 mg Fe/g dry weight is normal or near-normal, 7 mg/g marks the threshold above which complications accelerate, and values above 15 mg/g carry a high risk of cardiac disease and death. Trials typically report change in LIC at 6, 12 or 24 months as a primary or key secondary endpoint for chelation and for therapies that reduce transfusion burden.

Cardiac T2*: The Measurement That Changed Outcomes

Anderson and colleagues showed in 2001 that a multi-echo gradient-echo measurement of myocardial T2* in the interventricular septum identifies cardiac iron loading and that T2* below 20 ms indicates iron overload.[4] A subsequent prospective study of more than 650 patients demonstrated that T2* below 10 ms predicts a very high risk of heart failure within one year, which made cardiac T2* the trigger for intensified chelation.[5] Myocardial T2* was then directly calibrated against iron concentration in post-mortem hearts, confirming the relationship.[6] The in-

troduction of cardiac T2* screening is credited with a dramatic fall in cardiac mortality in thalassemia major.

International guidelines from the Thalassaemia International Federation recommend annual cardiac T2* and LIC assessment in transfusion-dependent patients, with more frequent imaging in those with T2* below 20 ms.[7] The same thresholds and schedules are used in trials to define eligibility, stratify risk and measure response.

New Therapies Raise the Stakes

The therapeutic landscape has changed quickly. Luspatercept, approved in 2019, reduces transfusion burden in beta-thalassemia; in its pivotal trial, significantly more treated patients than controls achieved at least a one-third reduction in transfusions.[8] Betibeglogene autotemcel, a lentiviral gene therapy, was approved in August 2022, and exagamglogene autotemcel, the first CRISPR-based therapy, in January 2024 for transfusion-dependent thalassemia; both aim at transfusion independence.[9,10] Mitapivat, an oral pyruvate kinase activator, was approved on December 23, 2025 for anemia in adults with alpha- or beta-thalassemia.[11] Each of these programs needs to show what happens to tissue iron when transfusions stop or fall: iron does not leave the body on its own, so LIC and cardiac T2* trends after treatment are critical secondary endpoints and long-term safety measures.

Technical Requirements for Trials

Iron MRI is quantitative only if acquisition is controlled. Protocols must fix field strength, echo times, flip angle and slice position; must avoid parallel imaging and fat-suppression settings that alter signal decay; and must specify the fitting model, including how to handle the signal plateau at very high iron where R2* exceeds measurable range at 3T. Phantom calibration across sites, central analysis by a single laboratory and documented reader reproducibility are expected by regulators for a primary imaging endpoint.[12]

Guidance for Sponsors

Imaging iron in a hematology trial

- **Pick the LIC method and stick to it.** R2 or R2*, with a single calibration applied for the entire trial.[1,2]
- **Always include cardiac T2*.** Ferritin and LIC do not predict cardiac iron; T2* under 20 ms defines overload and under 10 ms high risk.[4,5]
- **Specify the acquisition.** Field strength, echo train, flip angle, breath-hold and slice position fixed in the imaging charter.
- **Qualify sites with phantoms.** Confirm cross-site agreement before enrollment and after scanner upgrades.
- **Plan for post-transfusion-independence follow-up.** Gene and disease-modifying therapies need long-term iron trends.[9,10,11]
- **Analyze centrally.** One core lab, one fitting model, blinded readers.[12]

Summary

Quantitative iron MRI turned a lethal, invisible complication into a measurable and treatable one, and in doing so changed the survival of a generation of patients with thalassemia. For sponsors of chelators, disease-modifying agents and gene therapies alike, the message is the same: standardize acquisition, calibrate across sites and read centrally so that every milligram of iron measured means the same thing everywhere.

About the Author

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