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Guidance for Sponsors
Volume 6, Issue 5 · 2026 Edition

Advances in Imaging of Rheumatoid Arthritis

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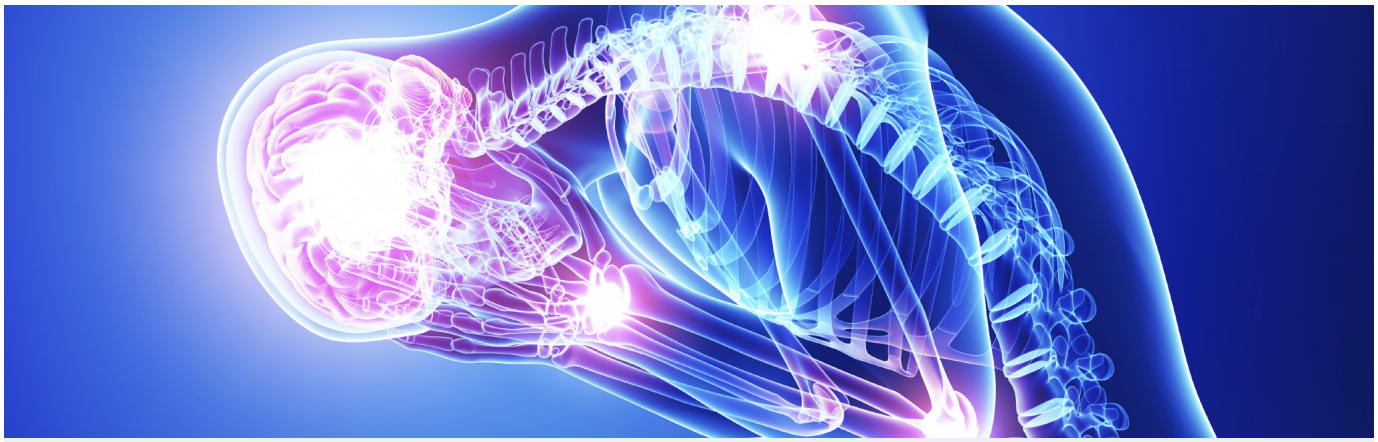

Rheumatoid arthritis (RA) affected an estimated 17.6 million people worldwide in 2020, and that number is projected to approach 32 million by 2050.[1] Biologic and targeted synthetic disease-modifying drugs have transformed outcomes, and every one of them reached the market with imaging evidence that it slows structural joint damage. Radiography remains the regulatory standard for that claim, but MRI and ultrasound detect inflammation and erosion months before radiographs change, and standardized scoring systems now exist for all three modalities. This issue reviews how imaging is used in RA trials and what a decade of imaging-guided treatment studies has taught sponsors.

The Disease and Its Imaging Signature

RA is a chronic autoimmune synovitis that preferentially attacks the small joints of the hands and feet. Inflamed synovium forms pannus that erodes cartilage and bone, producing the marginal erosions, joint-space narrowing and eventual deformity that define advanced disease. The 2010 ACR/EULAR classification criteria allow a diagnosis before erosions appear, which has shifted the goal of treatment to early intervention and remission before structural damage occurs.[2]

Imaging in RA therefore has two jobs: to detect and quantify inflammation (synovitis, tenosynovitis and bone marrow edema, now called osteitis) and to quantify structural damage (erosions and joint-space narrowing). Different modalities excel at different tasks.

Radiography: Still the Regulatory Standard

Plain radiographs of the hands, wrists and feet scored with the van der Heijde modified Sharp score remain the accepted method for demonstrating inhibition of structural progression. The score sums erosions and joint-space narrowing across defined joints, and trials report the change from baseline to 24 or 52 weeks. Radiography is insensitive to early disease and cannot see inflammation, but it is inexpensive, universally available and has decades of regulatory precedent. In practice, the challenges are standardization of positioning and exposure, chronological versus blinded-order reading, and the use of two trained readers with adjudication. Reader expertise matters: the smallest detectable change in the modified Sharp score is a few units, and poorly trained readers can double it.

MRI: Seeing Inflammation and Early Erosion

MRI depicts synovitis, tenosynovitis and osteitis directly and detects erosions well before they are visible on radiographs. Osteitis in particular predicts subsequent erosive progression and is a widely used mechanistic endpoint. The OMERACT RA MRI scoring system (RAMRIS) standardizes semi-quantitative scoring of synovitis, osteitis and erosions in the wrist and metacarpophalangeal joints; its 2017 update added joint-space narrowing and tenosynovitis to the core set.[3] Contrast-enhanced T1-weighted and fat-suppressed T2 or STIR sequences are standard. Dedicated extremity scanners at low and mid field strengths make MRI practical at many sites, while high-field 3T systems improve resolution for erosion assessment.

The EULAR recommendations on the use of imaging in RA endorse MRI and ultrasound for improving the certainty of diagnosis, detecting inflammation in clinically quiescent joints, and predicting progression, while recognizing that conventional radiography remains the first imaging technique for structural damage.[4]

Ultrasound: Fast, Dynamic and Now Standardized

High-frequency ultrasound with power Doppler shows synovial thickening and hyperemia in real time and can examine many joints in a single session. Its historical weakness was operator dependence. The EULAR-OMERACT ultrasound taskforce addressed this with a combined grayscale and power Doppler scoring system that defines synovitis grades 0 to 3 at the joint level and has demonstrated reliability across readers.[5] In trials, ultrasound is used for early detection, for enrichment of populations with active synovitis and as a sensitive secondary endpoint.

What the Imaging-Guided Strategy Trials Taught Us

An obvious hypothesis was that treating to an imaging target would produce better outcomes than treating to a clinical target. Three randomized strategy trials tested it. ARCTIC and TaSER used ultrasound remission as the target; IMAGINE-RA used MRI remission. None showed a meaningful improvement in clinical remission or radiographic progression over conventional clinical treat-to-target, and the imaging-guided arms used more biologic therapy.[6,7,8] For sponsors the lesson is specific: imaging is powerful for selecting patients, demonstrating mechanism and detecting structural change, but routine imaging-guided escalation in everyday care did not improve outcomes, so trial designs should use imaging as an endpoint and enrichment tool rather than as a treatment switch.

Guidance for Sponsors

Imaging a rheumatoid arthritis trial

- **Keep radiography as the structural anchor.** Modified Sharp score at baseline and 24 or 52 weeks, read by two trained readers with adjudication.[4]
- **Add MRI for mechanism and speed.** RAMRIS osteitis and synovitis scores change within weeks and predict erosion.[3]
- **Use standardized ultrasound.** Apply the EULAR-OMERACT combined score and define the joint set.[5]
- **Enrich, do not switch.** Use imaging to select active patients and measure change, not to drive treatment escalation.[6,7,8]
- **Fix the protocol.** Positioning, sequences, field strength and contrast must be consistent across sites and visits.
- **Read centrally.** Blinded independent review with documented reader reproducibility is the regulatory expectation.[9]

Summary

Imaging has made RA a disease that can be diagnosed early, treated before damage occurs and measured precisely. Radiography still carries the structural claim, MRI and ultrasound carry the mechanistic story, and the strategy trials have clarified where each belongs. Sponsors who use the modalities for what each does best will build cleaner trials and stronger submissions.

About the Author

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About Intrinsic Imaging, LLC

Intrinsic Imaging is an ISO certified medical imaging CRO and imaging core lab providing comprehensive services in support of Phase I-IV clinical trials and Class I, II, III medical device trials. Intrinsic Imaging is also a world leader in conducting Artificial Intelligence studies. With its team of more than 650 board-certified and fellowship-trained physicians, Intrinsic Imaging's team has sub-specialization in all therapeutic areas, including Cardiovascular, Central Nervous System,Gastroenterology, Musculoskeletal, Oncology and Ophthalmology. Certified by the British Standards Institution (BSI), Intrinsic Imaging is the only company in the world to hold five ISO certifications specifically for providing imaging core lab services on clinical trials. For more information, please visit www.IntrinsicImaging.com.

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