Osteoporosis Therapy: Challenges in Monitoring Efficacy in Clinical Trials

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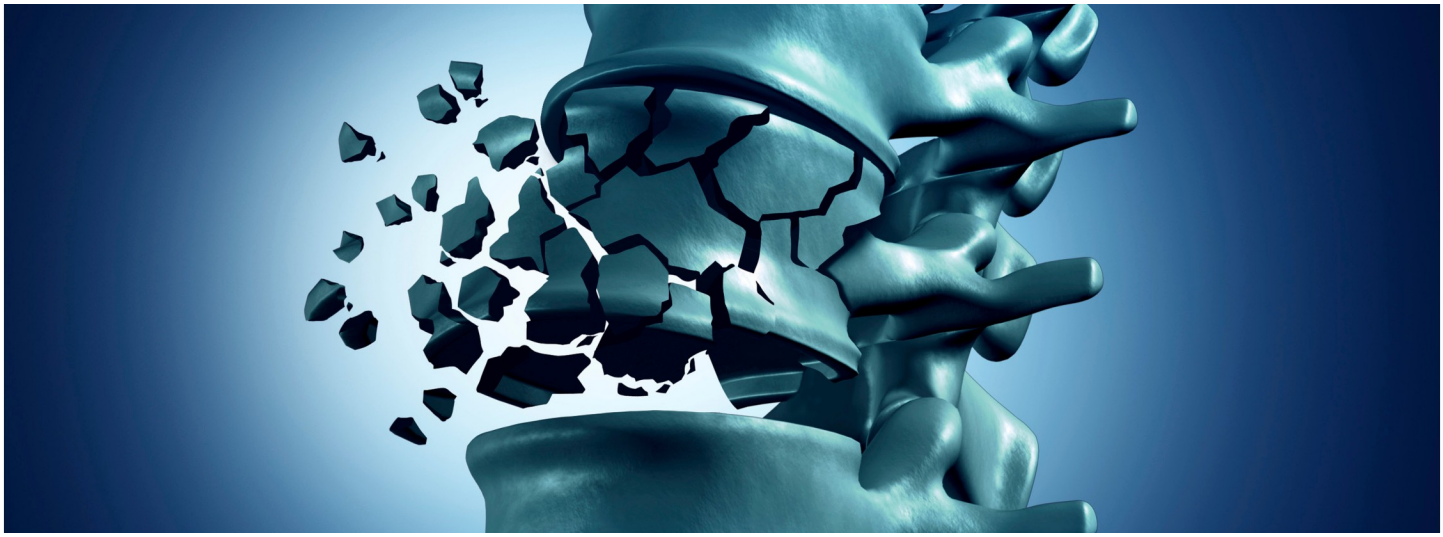

Osteoporotic fractures are devastating, and proving that a new therapy prevents them has traditionally required large, long fracture trials. That changed in December 2025, when FDA qualified the 24-month change in total hip bone mineral density (BMD), measured by DXA, as a validated surrogate endpoint for phase 3 trials in postmenopausal osteoporosis. The decision makes imaging quality more important than ever. DXA must be calibrated and centrally reviewed, while QCT, vertebral fracture assessment and microarchitecture imaging add information that BMD alone cannot provide.

Osteoporosis

A fracture late in life can be a sentinel event. Mortality in the year after a hip fracture in older patients can be as high as 20%. Hip fractures reduce mobility and increase the risk of deep venous thrombosis; vertebral fractures reduce thoracic and abdominal volume, impairing lung function and digestion; and fractures are linked to depression in older adults. Fragility fractures are not only a disease of women: an estimated 15 to 30% of men will sustain one in their remaining lifetime.

The link between fracture and low BMD is well documented. The World Health Organization defines osteoporosis as BMD 2.5 or more standard deviations below the mean peak bone mass of young healthy adults. Bone has two structural components: trabecular bone, the network of rods and plates in the medullary cavity that resists compressive and tensile forces, and the denser cortical bone that surrounds it. Both remodel constantly, but trabecular turnover is faster, so bone loss after menopause is greatest in trabecular-rich sites such as the vertebrae, proximal femur and distal forearm, the sites most prone to osteoporotic fracture. Low peak bone mass, reached around the fourth decade of life, is a major risk factor.

Therapy

Hormone replacement therapy was once the mainstay of treatment, but the Women's Health Initiative (2002) found that its benefits came with increased risks of thromboembolism, stroke, coronary disease and breast cancer. Selective estrogen receptor modulators such as raloxifene reduce vertebral fractures, with an increased risk of thromboembolism. Antiresorptive therapy is led by bisphosphonates, available in oral and intravenous forms, and by denosumab, a RANK ligand inhibitor. All bisphosphonates reduce vertebral fractures, though not all have shown reductions in non-vertebral fractures. Anabolic therapy now includes the parathyroid hormone analogs teriparatide and abaloparatide, and romosozumab, a sclerostin inhibitor approved by FDA in 2019 for postmenopausal women at high risk of fracture.[1] Calcium and vitamin D are widely used as adjuncts. No therapy is perfect, and trials continue in search of better treatments.

Dual-Energy X-ray Absorptiometry (DXA)

DXA passes x-rays of two energies through the body and calculates BMD from their differential attenuation. It is inexpensive, rapid, low-dose, widely available and highly reproducible on the same system. It also has limits. Most scans use a single anteroposterior projection, so spine BMD is falsely raised by degenerative endplate changes and osteophytes, aortic calcification, implants and the posterior vertebral elements. DXA measures areal BMD and does not distinguish trabecular from cortical bone. On the same equipment, the 95% confidence interval for a single BMD measurement is approximately 2.8%, comparable to the annual lumbar spine gain with bisphosphonate therapy, so meaningful monitoring is rarely possible more often than once a year.

A New Regulatory Endpoint

On December 19, 2025, FDA qualified the percentage change from baseline at 24 months in total hip BMD, assessed by DXA, as a validated surrogate endpoint for phase 3 trials of investigational therapies in postmenopausal women with osteoporosis at risk of fracture, providing an alternative to fracture endpoints.[2] The decision rests on the FNIH-ASBMR SABRE project, which analyzed 52 randomized trials involving more than 160,000 participants.[3] Trials can now be smaller, faster and less costly, but because the endpoint is a small change in a single measurement, the precision of DXA acquisition, calibration and analysis across sites becomes decisive. New morphometric vertebral fractures also remain an established basis for approval.[4]

Quantitative CT and Beyond

Quantitative computed tomography (QCT) measures true volumetric BMD in milligrams per cubic centimeter and separates trabecular from cortical bone, without the confounding structures that affect DXA. It can be applied to vertebrae and peripheral sites and expressed as T- and Z-scores. Because it isolates the metabolically active trabecular bone of the vertebral body, QCT predicts vertebral fracture with greater sensitivity than DXA, and dual-energy techniques further improve accuracy by accounting for marrow fat. Opportunistic analysis of CT scans obtained for other reasons is a growing area of research.[5]

Fracture is the ultimate endpoint. Vertebral morphometry identifies incident vertebral fractures, including those not clinically apparent, from standardized lateral images. Bone architecture contributes to fracture risk independently of BMD: high-resolution peripheral QCT and micro-CT assess trabecular and cortical microstructure, and high-resolution MRI may offer radiation-free assessment of bone quality.

Guidance for Sponsors

Imaging an osteoporosis trial

- **Design around the qualified endpoint.** For postmenopausal osteoporosis, consider 24-month total hip BMD change by DXA as a primary endpoint.[2]
- **Control DXA precision.** Use the same scanner per patient, daily phantom quality control, cross-calibration across sites and certified technologists.
- **Review every scan centrally.** Check positioning, region-of-interest placement and artifacts, and correct analysis errors consistently.
- **Capture vertebral fractures.** Include standardized lateral spine imaging and central morphometric assessment.[4]
- **Add QCT where it answers a question.** Use QCT or HR-pQCT for trabecular and cortical compartments or bone quality.[5]
- **Plan scan intervals around precision.** Space BMD measurements so expected change exceeds measurement error.

Summary

Osteoporotic fractures can be devastating, and better treatments are still needed. With total hip BMD now qualified as a surrogate endpoint, imaging has become the primary measure of efficacy in osteoporosis drug development. Choosing precise methods, standardizing them across sites and reviewing them centrally are now among the most important decisions in any osteoporosis trial.

About the Author

Dr. Lance Reinsmith, a board-certified radiologist specializing in orthopedic radiology and interventional pain management, wrote the original edition of this issue at Intrinsic Imaging. He received his M.D. from Baylor College of Medicine and completed residency training in diagnostic radiology at the Mallinckrodt Institute of Radiology, Washington University School of Medicine in St. Louis, where he also completed subspecialty training in musculoskeletal radiology and interventional spine procedures. He has presented research at meetings of the Radiological Society of North America and the American Society of Neuroradiology and has coauthored research published in *Radiology* and *RadioGraphics*.

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