

Each month the editor of *Newsline* selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. We have added a special section on molecular imaging, including both radionuclide-based and other molecular imaging efforts, in recognition of the extraordinary activity and promise of diagnostic and therapeutic progress in this area. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here.

THERAPY

α -RIT and Breast Cancer Metastases

In an article e-published on November 17 ahead of print in *Cancer Research*, Song et al. from the Johns Hopkins University School of Medicine (Baltimore, MD) and the Institute for Transuranium Elements (Karlsruhe, Germany) reported on the results of a study comparing the efficacy of ^{225}Ac -labeled monoclonal antibody (mAb) radioimmunotherapy (RIT) with similar RIT and the ^{225}Ac -daughter ^{213}Bi in a mouse model of breast cancer metastases. The researchers found that 1 administration of ^{225}Ac -labeled anti-rat HER-2/neu mAb completely eradicated breast cancer lung micro-metastases in two-thirds of HER-2/neu transgenic mice studied, with resulting long-term survival of up to 1 y for these responding mice. Radiolabeling the mAb with ^{225}Ac was found to be significantly more effec-

tive in terms of survival times and total doses than labeling with ^{213}Bi or ^{90}Y . The authors concluded that despite the high cost and half-life challenges of working with ^{225}Ac , “these data suggest ^{225}Ac -labeled anti-HER-2/neu monoclonal antibody could significantly prolong survival in HER-2/neu-positive metastatic breast cancer patients.”

Cancer Research

^{188}Re -ECD/Lipiodol in Hepatoma Treatment

Luo et al. from the Institute of Nuclear Energy Research (Taoyuan, Taiwan) reported in the October issue of *Cancer Biotherapy and Radiopharmaceuticals* (2009;24:535–541) on animal studies designed to evaluate the therapeutic potential of injection of ^{188}Re chelated with ethyl cysteinate dimer (ECD) in a lipiodol solution directly into hepatomas. A total of 39 rats were orthotopically implanted with hepatoma cells and divided into a treatment group ($n = 29$) that received ^{188}Re -ECD/lipiodol injected intratumorally and a control group ($n = 10$) that received saline injections. All rats were monitored for change in tumor size and survival times, and 3 rats in the treatment group also underwent SPECT/CT for biodistribution data. These data showed that activity was well retained in tumors for at least 24 h after injection. After 2 mo, rats in the treatment group had smaller tumor volumes and longer survival times than those in the control group (rates of 60% and 20% survival, respectively). The authors concluded that “ ^{188}Re -ECD/lipiodol via direct intratumoral injection shows potential for treating hepatoma and warrants further clinical trials.”

Cancer Biotherapy and Radiopharmaceuticals

Fractionated α -RIT in Ovarian Cancer

In an article e-published on October 25 ahead of print in the *Journal of Oncology*, Elqvist et al. from the

University of Gothenburg (Sweden) reported on a study investigating the therapeutic efficacy of different fractionated treatment regimens with α -emitter radioimmunotherapy (RIT) in ovarian cancer in mice. Mice ($n = 120$) were intraperitoneally inoculated with ovarian cancer cell lines. Four wk later, the mice were divided into 6 treatment groups of 18 animals each and 1 control group of 12. Treated animals were administered 400 kBq of a ^{211}At -labeled monoclonal antibody (mAb) (^{211}At -MX35 F(ab')₂) as a single dose or in treatments repeated up to 6 times. Fractionated treatments were given every 7th day. Control animals were treated with unlabeled mAb. After 8 wk, the mice were killed and evaluated for tumor burden and ascites. The percentages of animals with no macro- or microtumors and no ascites rose in direct relationship to the number of fractionated treatments received. The presence of ascites, for example, decreased from 15 of 18 animals in the group administered only a single treatment to 0 animals in the 2 groups administered 5 or 6 fractions. Treatment with the unlabeled mAb resulted in no animals free of tumors and ascites. The authors summarized their findings: “Weekly repeated intraperitoneal injections of tolerable amounts of activity of ^{211}At -MX35 F(ab')₂ of up to 6 times produced increased therapeutic efficacy without observed toxicity, indicating a potential increase of the therapeutic index.”

Journal of Oncology

MOLECULAR IMAGING/THERAPY

Adenoviruses Encoding Na/I Symporter

Peerlinck et al. from Queen Mary's School of Medicine and Dentistry (London, UK) reported in the November 1 issue of *Clinical Cancer Research* (2009;15:6595–6601) on

a study combining the imaging and therapeutic potential of the Na/I symporter (hNIS) with oncolytic antiviruses targeting colorectal cancer cells. In vitro and in vivo studies verifying the selectivity of the hNIS-encoding, Wnt-specific adenovirus (AdIP2) were conducted, and $^{99m}\text{TcO}_4^-$ SPECT/CT was used to monitor the injected agents spread to tumors in living mice. Forty-eight h after injection, mice received a single dose of $^{131}\text{I}^-$ administered intraperitoneally as metabolic radiotherapy. The authors found that this single therapeutic dose resulted in a dramatic reduction in tumor size not observed with hNIS-negative viruses. They concluded that “This report showed for the first time that the combination of the imaging and therapeutic potentials of hNIS can be applied to oncolytic adenoviruses in experimental models of cancer.”

Clinical Cancer Research

Imaging Angiogenesis in Osteosarcoma

In an article e-published on November 3 ahead of print in *Pediatric Blood and Cancer*, Bajpai et al. from the All India Institute of Medical Sciences (New Delhi) reported on a study exploring the utility of dynamic contrast-enhanced (DCE) MR and PET/CT imaging for quantitative and functional assessment of tumor angiogenesis in osteosarcoma. The study included 31 patients newly diagnosed with osteosarcoma who underwent both PET/CT and MR imaging before 3 cycles of neoadjuvant chemotherapy and surgery. Time/intensity curves (indicating microvascular permeability) were derived, and vascular endothelial growth factor (VEGF) expression was assessed in biopsies and resected specimens. Specimens were considered VEGF-positive when VEGF was observed in >10% of tumor cells. Time/intensity curves were found to correctly identify all 28 VEGF-positive specimens at baseline and 24 of 25 VEGF-positive samples and 5 of 6 VEGF-negative samples after chemotherapy. VEGF

expression was not correlated with diffusion-weighted MR or PET/CT results. The authors concluded that “This study suggests an important role of DCE MR imaging as a non-invasive imaging surrogate of tumor angiogenesis in osteosarcoma based on visual inspection of time/intensity curves.”

Pediatric Blood and Cancer

^{18}F -Labeled Knottin Peptide

In an article e-published on November 12 ahead of print in *Bioconjugate Chemistry*, Miao et al. from Stanford University (CA) reported on an engineered knottin peptide labeled with ^{18}F for PET imaging of integrin expression. Knottins (also called inhibitor cystine knots) are small, highly stable disulfide-rich proteins with a knotted topology that show promise for use as scaffolds for protein engineering and drug design. In a previous article, the authors’ research group reviewed the potential for knottins (*Cancer Res.* 2009;69:2435–2442) and have reported on the identification of a mutant knottin that binds to tumor-specific $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptors with low nanomolar affinity. In this study, the authors described the preparation and evaluation of a radiolabeled version of this knottin (called 2.5D) for microPET imaging of integrin-positive tumors in mice. Biodistribution and PET imaging were performed to evaluate the in vivo behavior of the ^{18}F -FB-2.5D compound. Moderate tumor uptake was seen at 0.5 h after injection, and PET indicated that the compound accumulated rapidly in the tumor and quickly cleared from the blood through the kidneys, facilitating excellent tumor-to-normal tissue contrast. The authors concluded that the “ ^{18}F -FB-2.5D allows integrin-specific PET imaging of U87MG tumors with good contrast and further demonstrates that knottins are excellent peptide scaffolds for development of PET probes with potential for clinical translation.”

Bioconjugate Chemistry

Molecular Phosphokinase Imaging and Gefitinib Response

Gong and colleagues from the University of Texas–M.D. Anderson Cancer Center (Houston) reported on December 2 ahead of print in *Cancer Biology and Therapy* on molecular imaging of gefitinib activity in an epidermal growth factor receptor (EGFR)–bearing xenograft model. The authors labeled an antiphosphotyrosine antibody with ^{111}In using ethylenedicysteine (EC) as a chelator to yield ^{111}In -EC-P-Tyr. A431 cells (human epithelial carcinoma cell line overexpressing EGFR) were xenografted in mice. Initial biodistribution studies indicated increased tumor-to-muscle ratios for the tracer in these mice. After gefitinib administration, imaging showed a marked decrease in tumor uptake of the radiolabeled compound. These results suggest that the compound can detect tumor phosphotyrosine kinase activity in vivo. The authors concluded that “This type of agent merits investigation in the clinic to determine if it can predict patient responses to kinase inhibitors based on phosphokinase imaging.”

Cancer Biology and Therapy

Monitoring Cellular Therapy in Stroke

In an article e-published on October 22 ahead of print in *Experimental Neurology*, Barbosa da Fonseca et al. from the Universidade Federal do Rio de Janeiro (Brazil) reported on successful migration, homing, and SPECT monitoring of intra-arterially injected bone-marrow mononuclear cells (BMMCs) in patients with chronic ischemic stroke. The study included 6 men between 59 and 82 d after ischemic cerebral infarct within the middle cerebral artery. Each patient received both unlabeled autologous BMMCs and a subset of ^{99m}Tc -labeled cells through a catheter navigated into the middle cerebral artery. At 2 h after injection, patients underwent whole-body scintigraphy, which showed cell homing in the

brain, with remaining uptake distributed to liver, lungs, spleen, kidneys, and bladder. Brain SPECT at the same time point showed preferential tracer accumulation in the hemisphere affected by the ischemic infarct in all patients. At 24 h after injection, this homing could be seen in only 2 of the patients. No patients showed adverse effects from the therapy at 4-mo follow-up. The authors concluded that “these results indicate that labeling of BMMCs with ^{99m}Tc is a safe and feasible technique that allows monitoring the migration and engraftment of intra-arterially transplanted cells for at least 24 h.”

Experimental Neurology

DIAGNOSIS

Stress-Only MPI

Chang et al. from the Methodist DeBakey Heart and Vascular Center (Houston, TX) reported on November 4 ahead of print in the *Journal of the American College of Cardiology* on a study designed to compare the prognostic information from a normal stress-only SPECT myocardial perfusion imaging (MPI) study with that from a standard stress/rest SPECT MPI study. The research included a retrospective review of all-cause mortality in 16,854 consecutive patients (47.6% of whom underwent stress-only and 52.4% of whom underwent both stress and rest imaging) with normal gated stress SPECT results and a median follow-up of 4.5 y. The overall unadjusted annual mortality rates were 2.57% in patients who had a normal SPECT with a stress-only protocol and 2.92% in those who also underwent rest imaging. Although this difference was not statistically different, the authors noted that the stress-only group received a 61% lower radiopharmaceutical dosage. The authors concluded that because patients with a normal SPECT on the basis of stress imaging alone have mortality rates similar to those of patients who have a normal SPECT on the basis of evaluation of both

stress and rest images, “additional rest imaging is not required in patients who have a normally appearing initial stress study.” In addition to cost and time savings, 1 result of omitting the rest study would be significant reductions in radiation exposure at a time of increasing patient concern about cumulative burden.

Journal of the American College of Cardiology

PET/CT-Guided IMRT in Cervical Cancer

In an article e-published on October 30 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics*, Kidd et al. from the Washington University School of Medicine (St. Louis, MO) reported on a study designed to evaluate toxicity and clinical outcomes in cervical cancer patients treated with PET/CT-guided intensity-modulated radiation therapy (IMRT) compared with non-IMRT treatment. The study included 452 women with newly diagnosed cervical cancer treated with curative intent (135 with IMRT and 317 with non-IMRT; the 2 groups had similar stage distribution and histologies). Treatment involved external irradiation and brachytherapy, and 85% of patients received concurrent chemotherapy. ^{18}F -FDG PET was used to provide a pretherapy simulation for those patients undergoing IMRT, and all patients underwent a PET/CT treatment response evaluation 3 mo after therapy. For all patients, post-therapy PET/CT results correlated with overall recurrence risk and cause-specific survival. Posttreatment PET findings were not significantly different between IMRT and non-IMRT patients. At last follow-up (mean = 52 mo), 39 IMRT and 139 non-IMRT patients had developed a recurrence. Although the difference in recurrence-free survival between the 2 groups was not statistically significant, the IMRT group showed better overall and cause-specific survival. Moreover, 54 non-IMRT and only 8 IMRT patients developed grade

3 or greater bowel or bladder complications. The authors concluded that “cervical cancer patients treated with FDG-PET/CT-guided IMRT have improved survival and less treatment-related toxicity compared with patients treated with non-IMRT radiotherapy.”

International Journal of Radiation Oncology, Biology, Physics

Toward Clinical RIMAs

Fowler and colleagues from the Brookhaven National Laboratory (Upton, NY) and the Mt. Sinai School of Medicine (New York, NY) reported on November 4 ahead of print in *Neuropsychopharmacology* on studies with reversible inhibitors of monoamine oxidase-A (RIMAs), which inhibit breakdown of the neurotransmitters serotonin, norepinephrine, and dopamine and thereby offer a number of potential strategies for treatment of depression. Focusing on CX1517, a RIMA currently in development for treatment of major depressive disorder, the authors used ^{11}C -clorgyline PET to serially assess degree and reversibility of inhibition of brain monoamine oxidase-A (MAO-A) and plasma tracer levels at different times after oral administration of CX1517. The study included 15 healthy men who received single or repeated doses of CX157 ranging from 20 to 80 mg. Higher doses (60–80 mg) produced a robust dose-related inhibition (47%–72%) of tracer binding to brain MAO-A at 2 h after administration, and brain MAO-A recovered completely by 24 h. The concentration of plasma CX157 was highly correlated with the inhibition of brain MAO-A. Data produced in the study will be used to establish a dosing regimen for a clinical efficacy trial with CX157, which the authors call “the first agent in the RIMA class with documented reversible inhibition of human brain MAO-A...and the first RIMA with observed plasma levels that can serve as a biomarker for the degree of brain MAO-A inhibition.”

Neuropsychopharmacology

Islet Grafting in a Bioengineered Intramuscular Space

Witkowski et al. from the Columbia University Medical College (New York, NY) reported in the November 15 issue of *Transplantation* (2009;88:1065–1074) on studies in rats designed to evaluate an intramuscular transplantation site for islet grafting, bioengineered to provide enhanced neovascularization, engraftment, and survival. ^{11}C -dihydrotetrabenazine PET was used to measure and follow the transplanted β -cell mass in real time. After receiving streptozotocin, which selectively destroys pancreatic β -cells, rats were pretreated intramuscularly with a biocompatible angiogenic scaffold. Two wk later, the rats received syngeneic islet transplants and were monitored by laboratory studies, histopathologic assessments, and PET imaging of the transplant site. Transplantation-induced reversal of hyperglycemia was more successful in recipients pretreated with bioscaffolds with angiogenic factors than in those that received no bioscaffolds or bioscaffolds without angiogenic factors. PET imaging, insulin staining, and microvascular density patterns were all directly correlated with islet survival, increased angiogenesis, and reversal of hyperglycemia. These data suggest that the use of a nonhepatic transplant site may avoid the intrahepatic complications often noted in conventional transplantation and permit the use of PET imaging to measure and monitor transplanted β -cell mass in real time. The authors concluded that “These findings have important implications for effective islet implantation outside of the liver and offer promising possibilities for improving islet survival, monitoring, and even prevention of islet loss.”

Transplantation

^{124}I -PET/CT in rhTSH vs Thyroid Hormone Withholding

In an article e-published on October 23 ahead of print in *Experimental and Clinical Endocrinology and Di-*

abetes, Freudenberg et al. from the University of Duisburg/Essen (Germany) reported on a ^{124}I PET/CT comparison of recombinant human thyroid-stimulating hormone (rhTSH) administration and thyroid hormone withholding before radioiodine remnant ablation in differentiated thyroid cancer. The retrospective study included the records of 55 consecutive totally thyroidectomized, radioiodine-naïve patients. The patients were divided into 2 groups based on treatment: 16 patients in the rhTSH group received ^{124}I administration 24 h after 2 consecutive daily intramuscular injections of rhTSH, and 39 patients in the thyroid hormone withdrawal group received ^{124}I after several weeks of thyroid hormone withdrawal. PET was performed on all patients at 4, 24, 48, 72, and 96 h after tracer administration, and PET/CT was performed at the 25-h mark. Median stimulated serum thyroglobulin was found to be 15 times higher and M1 disease almost twice as prevalent in rhTSH patients as in the thyroid hormone withdrawal group. Mean radiation dose of administered ^{131}I activity was statistically equal between the 2 groups. The authors concluded that because rhTSH and thyroid hormone withdrawal deliver statistically equivalent radiation doses to thyroid remnant, either approach could be selected “based on safety, quality of life, convenience, and pharmacoeconomic factors” and that institutional fixed radioiodine activities formulated for use with thyroid hormone withdrawal do not need to be adjusted for rhTSH-aided ablation.

Experimental and Clinical Endocrinology and Diabetes

Myocardial Perfusion SPECT in the Elderly

Hachamovitch and colleagues from the Cedars-Sinai Medical Center (Los Angeles, CA), Albert Einstein Medical Center (Philadelphia, PA), and the University of Arizona College of Medicine (Tucson) reported on November 16 ahead of print in *Circulation* on a study assessing the prognostic

implications and clinical value of myocardial perfusion SPECT (MPS) in elderly individuals. The study followed almost 5,200 patients who were older than 75 y after dual-isotope MPS for an average of almost 3 y and a subset (684 patients) for more than 6 y. Survival analyses of cardiac deaths indicated that findings of both MPS-measured ischemia and fixed defect added incrementally to preimaging data in patients undergoing either adenosine or exercise stress. In a subset with gated scintigraphy ($n = 2,472$), ejection fraction and perfusion data added incrementally to enhancing risk stratification. Normal MPS cardiac death rates in the study were approximately one-third lower than the baseline risk of age-matched U.S. individuals. The extended follow-up studies showed an interaction between early treatment and ischemia, with increasing ischemia associated with increased survival/early revascularization and medical therapy associated with improved outcomes in patients with no or little ischemia. The authors concluded that “stress MPS effectively stratifies cardiac death risk in elderly patients and may identify optimal post-MPS therapy.”

Circulation

Dopamine Receptors and Bariatric Surgery

In an article e-published on October 29 ahead of print in *Obesity Surgery*, Steele et al. from the Johns Hopkins University School of Medicine (Baltimore, MD) reported on a preliminary study to investigate dopamine D_2 receptor activity in obese women before and after laparoscopic Roux-en-Y gastric bypass (LGBP) surgery. The study included 5 women (20–38 y old, mean body mass of 45) who underwent ^{11}C -raclopride PET imaging before and 6 wk after LGBP. Regions of interest analyzed were the ventral striatum, anterior and posterior putamen, and anterior and posterior caudate nucleus. Results were compared with a database of findings in nonobese controls. D_2 receptor availability was found to

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increase at 6 wk after bariatric surgery and appeared to be proportional to the amount of weight lost in the interim. These and other data led the authors to conclude that “brain available dopamine D₂ binding appears to increase following gastric bypass surgery,” which “suggests that diminished D₂ binding in the obese may be due to D₂ receptor downregulation” and that “changes in available dopamine receptor binding may play an important role in centrally mediated appetite suppression and resultant weight loss after LGBP.”

Obesity Surgery

PET and Scintigraphy in Paraganglioma

Timmers and an international consortium of colleagues from the United States and Europe reported on October 28 ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on an assessment of optimal approaches to functional imaging of pheochromocytoma and paraganglioma, including a comparison of the relative efficacies of ¹⁸F-fluoro-L-DOPA PET, ¹⁸F-FDG PET/CT, ¹⁸F-fluorodopamine (¹⁸F-FDA) PET/CT, ¹²³I-MIBG scintigraphy, CT, and MR. The study included 52 patients (28 males, 24 females; 20 with non-metastatic paraganglioma [11 adrenals], 28 with metastatic paraganglioma [13 adrenal], and 4 in whom paraganglioma was ruled out). Twenty-two of the paragangliomas were of the succinate dehydrogenase subunit B (SDHB) ge-

notype. Sensitivity for localizing paragangliomas was assessed for the 3 types of PET, as well as scintigraphy, CT, and MR. Sensitivities for localizing non-metastatic paraganglioma were 100% for CT and/or MR, 81% for ¹⁸F-DOPA PET, 88% for ¹⁸F-FDG PET/CT, 78% for ¹⁸F-FDA PET/CT, and 78% for ¹²³I-MIBG scintigraphy. For metastatic paragangliomas, sensitivity compared with CT/MR was 45% for ¹⁸F-DOPA PET, 74% for ¹⁸F-FDG PET/CT, 76% for ¹⁸F-FDA PET/CT, and 57% for ¹²³I-MIBG scintigraphy. ¹⁸F-FDA and ¹⁸F-FDG were found to have higher sensitivities (82% and 83%, respectively) than ¹²³I-MIBG (57%) and ¹⁸F-DOPA (20%) in patients with SDHB metastatic paraganglioma. The authors concluded that although ¹⁸F-FDA PET/CT is the preferred technique for localization of a primary paraganglioma and to rule out metastases, ¹⁸F-DOPA PET and ¹²³I-MIBG scintigraphy are equally adequate second choices. They added significant recommendations on genotype-selective imaging: “For patients with known metastatic paraganglioma, we recommend ¹⁸F-FDA PET in patients with an unknown genotype, ¹⁸F-FDG or ¹⁸F-FDA PET in SDHB mutation carriers, and ¹⁸F-DOPA or ¹⁸F-FDA PET in non-SDHB patients.”

Journal of Clinical Endocrinology and Metabolism

MR and PET in Myocardial Oxygenation in CAD

In an article e-published on November 17 ahead of print in *Cir-*

culation, Cardiovascular Imaging, Karamitsos et al. from the University of Oxford (UK) reported on a study using MR and PET to assess the relationship between regional myocardial oxygenation and perfusion in patients with coronary artery disease (CAD). The study included 22 patients (16 men, 6 women; ages 62 ± 8 y) with CAD (at least 1 stenosis ≥ 50% on quantitative coronary angiography) and 10 normal volunteers (6 men, 16 women; ages 58 ± 6 y), each of whom underwent 3T blood oxygen level-dependent (BOLD) cardiovascular MR to measure myocardial oxygenation and O₁₅-water PET for myocardial blood flow (MBF) quantification. Both imaging modalities were used at rest and in adenosine stress. BOLD CMR and PET findings agreed on the presence or absence of ischemia in 18 of the 22 patients (82%) and in all volunteers. On a per-segment analysis, 40% of myocardial segments with stress MBF below a cutoff of 2.45mL/min/g did not show deoxygenation, whereas 88% of segments with normal perfusion also had normal oxygenation measurements. The authors concluded that these results suggest that “regional myocardial perfusion and oxygenation may be dissociated, indicating that in patients with CAD reduced perfusion does not always lead to deoxygenation.”

Circulation, Cardiovascular Imaging

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metastases improve health outcomes of beneficiaries with cancer. Therefore CMS proposes that this use is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the Act).” However, CMS indicated that available evidence is sufficient to determine that Na¹⁸F PET imaging can identify bone metastasis of cancer for the purpose of informing the initial antitumor treatment strategy or guiding subsequent antitumor treatment strategy after completion of initial treatment. CMS proposed to cover Na¹⁸F PET imaging when the beneficiary’s treating physician determines that the PET study is needed for these purposes and when the beneficiary is enrolled in (and the Na¹⁸F PET provider is participating in) the following type

of prospective clinical study: “An Na¹⁸F PET clinical study that is designed to collect additional information at the time of the scan to assist in initial treatment planning and in identification of symptomatic bone metastases.” Qualifying clinical studies must ensure that specific hypotheses are addressed, appropriate data elements are collected, hospitals and providers are qualified to provide the PET scan and interpret the results, participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms, and all patient confidentiality, privacy, and other federal laws must be followed.

*Centers for Medicare & Medicaid Services
SNM*