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The Honorable Mark McClellan
Administrator
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Hubert H. Humphrey Building
ROOM 445-G
200 Independence Avenue, S.W.
Washington, DC 20201

Re: Guidance for Coverage with Evidence Development

Dear Administrator McClellan:

The Academy of Molecular Imaging (AMI) submits these comments on the Centers for Medicare and Medicaid Services (CMS) guidance document entitled "National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development," issued on July 12, 2006. As the principal architect of two of the first coverage with evidence development (CED) initiatives—the National Oncologic PET Registry (NOPR) and the Metabolic Cerebral Imaging in Incipient Dementia (MCI-ID) trial—AMI offers an unique perspective on the practical implementation of CED. AMI remains a strong advocate of CED, and appreciates CMS's efforts to refine and clarify its policy. In this comment, AMI requests that CMS issue additional guidance in order to assist both registry sponsors and the agency itself in determining when to terminate data collection requirements imposed pursuant to CED.

The National Oncologic PET Registry

In January 2005, CMS announced that it would expand Medicare coverage for positron emission tomography (PET) with 2-[^{18}F]flouro-2-deoxyglucose (FDG) for the diagnosis and management of patients with malignancies. The decision followed many years of incremental expansion of Medicare coverage for oncologic applications of PET, and was conditioned on the collection of prospective clinical and demographic data on Medicare beneficiaries receiving PET scans under this policy.

After a lengthy period of project design and regulatory review by the Department of Health and Human Services (DHHS), the NOPR, a nation-wide prospective internet-based registry, went into operation in

May 2006. Detailed information on the NOPR is available at http://www.cancerpetregistry.org. Medicare beneficiaries who are referred for PET for an oncologic indication that is either not currently covered or not specifically non-covered by Medicare are eligible to participate. The primary scientific objective of the registry is to assess the effect of PET on referring physicians' intended patient management across the spectrum of the expanded cancer indications.

Because DHHS does not consider the submission of data to the NOPR by individual PET facilities and referring physicians to constitute research, they are not required to obtain institutional review board (IRB) approval. As the NOPR Operations Manual explains, "[t]he only entity engaged in research is the registry itself (i.e., NOPR)." The IRB for the American College of Radiology Information Network—the organization that is administering the NOPR—has approved the use of the data for research purposes. Both patients and referring physicians are considered research subjects, however, and must therefore provide informed consent before their data can be used for research. Either before or upon arrival at a PET facility, each patient receives a standard NOPR information document describing the registry and requesting that the patient provide oral consent for the use of his or her identified data for research purposes. If the patient withholds consent, his or her identified data is still collected by the PET facility, sent electronically to the NOPR, and submitted to CMS for the purpose of determining payment; however, the data is not used for research.

Participating PET facilities use a secure, internet-based application to register patients referred for NOPR-eligible indications and to submit other required information to the NOPR database. Before the PET scan, the referring physician must complete a *Pre-PET Form* providing, among other data, the following information: (1) the specific reason for the PET referral; 2) the cancer type (if known) and an assessment of the working stage; (3) the patient's performance status; (4) the physician's intended management plan for the patient if PET were not available; and (5) whether the referring physician is also the treating physician. This form must be returned to the PET facility, and the PET facility staff must enter the data into the registry no later than the day of the PET scan.

After the PET scan is performed and the PET report is entered into the database, the referring physician must complete an indication-specific *Post-PET Form* in order to assess the physician's intended patient management in light of the PET findings. The *Post-PET Form* also solicits consent from the referring physician to allow his or her response data to be used for research purposes. Physicians who elect to withhold consent nevertheless must submit all of the required data elements as a condition of reimbursement by CMS; however, that data is excluded from the research dataset used by NOPR investigators. When all of the required forms have been entered into the NOPR database, the registry notifies the PET facility that it can submit its claim to CMS. In order for the case to be eligible for reimbursement by Medicare, all required data must be entered into the registry within 30 days of the PET scan

The NOPR began accepting patient registrations on May 8, 2006. As of August 8, 2006, 1,185 PET facilities nationwide were participating in the registry, 7,020 patients had been registered, and complete data for 5,586 had already been submitted. Patients and referring

physicians have consented to the use of data for research purposes in approximately 92% and 96% of cases, respectively.

FDG-PET for Early Diagnosis of Alzheimer's Disease

In addition to sponsoring the NOPR, AMI has also been involved in one of the first CED initiatives involving a clinical trial. In an NCD for FDG-PET for Dementia and Neurodegenerative Diseases (220.6.13), CMS indicated that an FDG-PET scan is considered reasonable and necessary in patients with mild cognitive impairment or early dementia only in the context of an approved clinical trial that contains patient safeguards and protections to ensure proper administration, use and evaluation of the FDG-PET scan.

University of California at Lost Angeles will administer the Metabolic Cerebral Imaging in Incipient Dementia (MCI-ID) trial. Although CMS authorized a CED study for dementia and neurodegenerative disease more than 18 months ago, due to administrative and funding challenges the MCI-ID trial has yet to begin operation. As discussed below, the MCI-ID trial illustrates some of the complexities of translating a CED policy into a clinical study.

Importance of Stakeholders in Developing and Implementing CED Policy

CMS's revised guidance document reflects its experience with these early CED initiatives. In particular, the agency has made clear that that it does not intend to fund, "routinely develop, oversee, or maintain these databases or registries that contain information about provision of an item or service." As a result, most of the logistical, administrative and financial support for data registries will have to come directly from stakeholders. In fact, AMI funded the initial cost of designing the NOPR, and collaborated with a host of other stakeholders—including the American College of Radiology, the American Society of Clinical Oncology, and the Society for Nuclear Medicine—on its design and implementation.

The experience of trial sponsors both with the NOPR and the MCI-ID trial highlight the importance of close cooperation between trial sponsors and CMS. In order to avoid undue delays and unnecessary administrative hurdles, it is critical that CMS consult closely with registry sponsors in implementing and refining CED policy.

Ending CED-Required Data Collection

A primary issue of concern for AMI is how long the NOPR will remain in operation. The recent guidance does little to clarify for the sponsors and administrators of CED registries when and how data collection requirements will be terminated. Specifically, the guidance states that for registries collecting data under coverage with appropriateness determination, CMS will evaluate the data on an ongoing basis to determine when the collection effort has satisfied the data requirements of the national coverage decision (NCD). For registries collecting data under coverage with study participation, the collection requirement endures until the hypothesis upon which the registry is based can be satisfied. In both cases, the data collection requirement is very open-ended.

CED registries entail substantial financial and administrative burdens for their sponsors. As CMS states in the guidance, the agency generally does not fund the non-clinical research costs involved in the development and maintenance of CED registries. And indeed, both the NOPR and the Implantable Cardioverter Defibrillators (ICD) registry—the first two operational CED registries—have depended heavily on industry sponsorship. Registries must contract for various services and supplies, as well as maintain their own staff of administrative employees. The NCDs authorizing CED registries therefore should include clear, objective standards for determining when the collection requirement will end. In some cases, the NCD may sunset the data collection requirement at a date certain. This would provide the sponsors and administrators of CED registries with a crucial measure of predictability.

In the guidance, CMS lists four factors that the agency will consider in determining whether to conclude a data collection requirement:

1. Data from the registry provides satisfactory answers to the questions posed in the NCD that were used to establish the registry.

2. Stronger evidence of a health benefit of the item or service published in peer-reviewed literature after the original NCD.

3. Evidence that the item or service does not provide a health benefit in the long term.

4. Evidence of an unacceptable level of adverse events beyond that found in the published literature during the NCD analysis.

AMI is concerned that this guidance is not sufficiently specific to permit registry sponsors and providers to engage in the kind of planning that is required for the administration of a CED registry. AMI is also concerned that the subjective nature of the criteria leave them vulnerable to selective application.

It is not feasible to publish a peer-reviewed study for each and every NOPR-eligible indication. CMS therefore should not require, as a condition of regularizing coverage, a separate published, peer-reviewed study demonstrating that PET is reasonable and necessary for every application. Such a requirement would only reproduce the pre-NOPR gaps in coverage, and further compromise access for Medicare beneficiaries.

AMI would like to meet with CMS at the beginning of 2007 to review the initial data from the NOPR. AMI expects that by 2007 there will be publications based on data from the NOPR submitted to peer-reviewed journals for several specific cancer indications. CMS should undertake a wholesale reconsideration of the January 28, 2005 NCD based on data collected on ***all*** of the NOPR-eligible indications. Such a reconsideration should assess whether the registry has answered its research questions, and determine whether the data thus collected warrants lifting the previous non-coverage policy. AMI expects that the NOPR will require two to three

years to develop data and three to four years to generate published literature sufficient to support coverage for all oncologic applications of PET covered by the registry.

PET for Bone Imaging and Infection Imaging

AMI wishes to emphasize that the current CED initiatives for PET, as well as the NCD authorizing these initiatives, are specific for the oncologic applications of PET conducted with the radiopharmaceutical FDG. The first NCD for FDG-PET, issued on December 15, 2000, was entitled "Position Emission Tomograph (FDG)." (CAG-00065N). CMS has issued eight subsequent NCDs that apply explicitly only to FDG-PET, and one NCD for N-13 Ammonia.

More recently, a growing body of literature has demonstrated the utility of FDG-PET and PET/CT as diagnostic tools for detecting infections,[1] especially in patients with fever of unknown origin and in those with osteomyelitis after various orthopedic interventions.[2] In addition, there is currently much interest in using PET and PET/CT with F-18 fluoride for bone imaging,[3] and the available literature indicates that this is an exquisitely sensitive method for detection of osseous metastatic disease and other skeletal disorders. Both FDG-PET for infection imaging and F-18 fluoride PET for bone imaging are strong candidates for CSP trials. AMI will prepare NCD requests to submit to CMS for these procedures.

As always, AMI would welcome the opportunity to work with agency staff to further improve CED.

Sincerely,

R Edward Coleman

Dr. R. Edward Coleman
Immediate Past President
Academy of Molecular Imaging

[1] *See* Eur. J. Nucl. Med. Imaging 33:913-6, 2006.
[2] *See* Nucl. Med. Comm. 27:633-44 and 645-60, 2006.
[3] *See* J. Nucl. Med. 40:1623-29, 1999; J. Bone Miner. Dis. 18:2206-14, 2003.