1300 North 17th Street ▪ Suite 900

Arlington, Virginia 22209Tel: 703.841.3200

www.medicalimaging.org

Via Electronic Submission

February 8, 2022

The Honorable Chiquita Brooks-LaSure
Administrator
Centers for Medicare & Medicaid Services
7500 Security Blvd
Baltimore, MD 21244

RE: Proposed Decision Memorandum: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N)

Dear Administrator Brooks-LaSure:

As the leading trade association representing the manufacturers of medical imaging equipment, radiopharmaceuticals, contrast media, and focused ultrasound therapeutic devices, the Medical Imaging & Technology Alliance (MTA) strongly disagrees with the Centers for Medicare & Medicaid Services' (CMS) proposal to restrict coverage of anti-amyloid monoclonal antibodies (mABs) for Alzheimer's treatment to approved clinical trials under Coverage with Evidence Development (CED). We are concerned that the Proposed Decision Memorandum (PDM) requirement of coverage limited to randomized controlled trials (RCTs) in the hospital outpatient setting will significantly restrict and delay beneficiary access. Although MITA supports CMS' proposal to cover an amyloid PET scan where included in an approved CED, we believe CMS should remove the limitation to one scan, and the link to any existing CED with the inclusion of amyloid PET. Further, we request CMS promptly fast track coverage approval for amyloid PET at the same time as the Decision Memorandum for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. **It is appropriate to cover amyloid PET given the body of evidence that has accumulated over a decade from CMS-approved and other clinical studies**.

MITA appreciates the opportunity to provide public comments in response to CMS' PDM for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N PDM). The PET Group within MITA is a collective voice of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) radiopharmaceutical developers, manufacturers, and distributors. Advances in nuclear medicine allow clinicians to more effectively identify and target disease, thereby providing more options for treatment resulting in better patient outcomes. Advances have been made in cancer, heart disease, Alzheimer's pathology and in other areas. In some cases, there are no alternative diagnostics.

Based on MITA's prior experiences with the use of CED for PET imaging, we believe that the PDM will significantly restrict and delay beneficiary access to the first FDA-approved therapy for Alzheimer's disease in two decades and the products that will soon follow.

- It took 18 months from the issuance of the Decision Memorandum for beta amyloid PET imaging in September 2013 until the protocol for the "Imaging Dementia—Evidence for Amyloid Scanning (IDEAS)" CED study was approved by CMS, and another 11 months for the first patients to be enrolled in the study. This amounted to a delay of almost two and a half years for the first Medicare beneficiary to receive access.
- Another significant delay occurred between the closing of IDEAS and initiation of the follow-on CED Study, New IDEAS. The IDEAS Study Team presented a follow-on protocol using the same operational infrastructure and yet this study required significant time for CMS approval, resulting in another 23-month gap in patient access to beta amyloid PET scans.
- Additionally, since CMS has no requirement to reconsider CED decisions based on new data, appropriate beneficiary access may be further delayed. MITA members submitted a reconsideration request for beta amyloid PET in September 2020; however, there has been no formal response from CMS to this reconsideration request.

Finally, the PDM would preemptively limit coverage for the entire class of anti-amyloid mABs before other products of the class have been reviewed and approved by the FDA. It is unprecedented for CMS to require CED for a therapeutic before a full dossier is available and treatment has been approved by the FDA. The restrictive CED criteria proposed by CMS would exacerbate access disparities along geographic, racial, and socioeconomic lines.

I. Recommend Coverage of Beta Amyloid PET Imaging

MITA has submitted literature to CMS demonstrating that beta amyloid PET imaging is reasonable and necessary for its FDA-approved labeled indications, including determining whether a beneficiary is a candidate for an anti-amyloid mAB for Alzheimer's. Beta amyloid PET imaging should be covered without a CED requirement.

Nearly a decade after the September 2013 Decision Memorandum establishing CED for beta amyloid PET, there is considerable published evidence that the use of beta amyloid PET imaging positively impacts patient management and leads to changes in diagnosis. Data from the IDEAS Study show that beta amyloid PET scans led physicians to change their management in more than 60% of patients, whether they had mild cognitive impairment (MCI) or dementia. Moreover, 35.6% of patients with MCI and dementia received a change in diagnosis following the PET scan and 36.1% of patients who were considered to have Alzheimer's disease after the clinical assessment and before the PET scan were found to be amyloid negative. This underlines the important role that beta amyloid PET scans play in the diagnostic workup of patients with cognitive impairment, especially for ruling out an incorrect etiologic diagnosis. *See* Rabinovici, G. et al. "Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia," JAMA 2019; 321(13):1286-1294.

These results demonstrate that the use of beta amyloid PET improves the care patients receive and reduces utilization of the most expensive types of healthcare. Based on these and similar data, we once again urge CMS to resolve the persistent access issues under the current NCD for beta amyloid PET by fast tracking coverage of beta amyloid PET at the same time as the Decision Memorandum for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease.

While we believe that coverage should not be limited to CED, we agree with the agency's proposal to cover beta amyloid PET imaging in "any CMS approved trials, or trials supported by the NIH, that include a beta amyloid positron emission tomography (PET) scan as part of the protocol." MITA understands the proposed coverage of a beta amyloid PET scan under the PDM to mean that if a scan is included in the clinical trial protocol, it will be covered **regardless** of whether the result of the scan is positive or negative, and whether it results in the beneficiary qualifying for administration of the anti-amyloid mAB product. Section B of the Proposed Decision includes no qualifier limiting coverage based on the results of the scan. We support this interpretation and believe, as a general matter, that including beta amyloid PET scans in CED studies will be important to limit utilization of anti-amyloid mABs to those beneficiaries who may benefit from the drugs.

MITA strongly disagrees with CMS' proposal to limit coverage to "one beta amyloid PET scan…if the patient did not previously receive a beta amyloid PET scan." Where a study protocol calls for multiple beta amyloid scans, CMS should not interject itself into clinical decision-making by refusing to cover a subsequent scan. A single-scan coverage limitation is particularly problematic when the patient may have had a negative scan in the past, and when the objective of the study is to assess the clinical utility of an anti-amyloid therapy. At minimum, coverage should include a follow-up scan to determine the extent of plaque removal as a result of mAB therapy.

Finally, we note that CMS is proposing to require that "[a]ll trials must be conducted in a hospital-based outpatient setting." Although we are concerned about this outpatient requirement for reasons outlined in Section II, we understand the requirement to mean that the **mAB therapy** must be administered in the hospital outpatient setting, while the beta amyloid PET scan may be performed at a freestanding Independent Diagnostic Testing Facility (IDTF). The IDEAS Study demonstrated that approximately 70% of the amyloid PET scans were conducted at IDTFs. Beneficiaries should be allowed to access advanced imaging where it is available and most convenient.

Additionally, we oppose any type of limitation that the scan must be performed in the hospital outpatient setting due to CMS' policy of packaging payment for beta amyloid PET. The current payment policy creates a disincentive for hospitals to provide beta amyloid PET scans, which could further exacerbate access disparities both to beta amyloid PET and to anti-amyloid mABs in the context of a CED study that requires a beta amyloid PET scan to access the therapeutic.

II. Proposed CED for Anti-Amyloid mABs Would Severely Restrict Access

MITA is concerned about the PDM's proposal of coverage with evidence development limited to RCTs and trials supported by the National Institutes of Health (NIH). The extremely narrow coverage criteria in CMS' CED proposal would severely restrict access for beneficiaries to FDA-approved therapies when there are no other treatment options for Alzheimer's.

The PDM's requirement that anti-amyloid mABs for the treatment of Alzheimer's are covered only in the context of a RCT will further exacerbate beneficiary access limitations and discrepancies. The RCT requirement would equate to a non-coverage determination for the near future, given the length of time required to develop a RCT protocol and secure CMS approval. This will deny access to the considerable number of patients for whom anti-amyloid mABs may now be indicated as an FDA-approved therapy, but who may experience decline sufficient to make the therapy no longer appropriate by the time a RCT is enrolling. Furthermore, a RCT in which a randomly selected control group of Alzheimer's patients is

denied access to a therapy determined by the FDA to be safe and effective may present significant ethical difficulties.

The requirement that "[a]ll trials must be conducted in a hospital-based outpatient setting" is also highly problematic from an access perspective. Hospital-based RCTs are feasible primarily for academic medical centers, meaning that CED-eligible trial sites will be concentrated at such centers under the PDM's coverage criteria. Accordingly, the agency's proposal risks concentrating access to anti-amyloid mABs, for the foreseeable future, among people who live in major metropolitan areas or who have the resources to frequently travel to those areas.

The concentration of CED trials at major academic medical centers engendered by the agency's proposal could worsen existing disparities in Alzheimer's treatment against minority racial and ethnic groups, socioeconomically disadvantaged Americans, and persons residing in rural areas. This result would be in direct conflict with subsection C.2(c) of the Proposed Decision's requirement that "[t]he diversity of patients included in each trial must be representative of the national population diagnosed with AD." It would similarly conflict with the requirement of the National Alzheimer's Project Act (NAPA) (42 USC § 11225) that the Department of Health and Human Services (HHS) "ensure the inclusion of ethnic and racial populations at higher risk for Alzheimer's or least likely to receive care, in clinical, research, and service efforts with the purpose of decreasing health disparities in Alzheimer's."

Recent CED studies have shown the difficulty of enrolling members of underserved communities (including minority ethnic and racial groups) in clinical trials, even absent mandatory requirements for site of care and enrollment levels. CMS should ensure that its policy is flexible and lowers barriers to access and does not add additional obstacles as currently proposed by the agency. The New IDEAS study, which was approved in April 2020, was established for the specific purpose of recruiting members of minority ethnic and racial groups, given that these demographics comprised less than 3% of the original IDEAS population. The IDEAS study team retained minority recruitment centers of excellence who could bring best practices and learnings to bear on trial operations and engaged in a proactive and purposeful strategy to recruit these underserved populations as well as overcome cultural barriers of clinical trial participation. Minority populations are difficult to recruit into clinical trials due to systemic and cultural issues that are not easily remedied, and it takes significant time to build relationships, engage in community networks, tailor materials and strategies and address issues of cost, transportation, and access. Despite this concerted effort, minority recruitment goals are still lagging more than one year after patient enrollment opened. Given these considerations, instead of adding to the difficulties of trial sponsors in recruiting members of minority ethnic and racial groups through a rigid RCT and outpatient setting requirement, CMS should, instead, outline the clinical qualifications of participating trial sites and make trial participation open to any sites that meet these criteria.

Finally, in MITA's longstanding experience with CED, the requirements have been time and resource intensive and created significant beneficiary access delays. CMS' September 2013 Decision Memorandum (CAG-00431N) established a CED requirement for beta amyloid PET. The first CED trial was not approved under this NCD until April 2014. Moreover, this first CED study was a small, 117 participant study on the "Effect of Aerobic Exercise on Pathophysiology in Preclinical Alzheimer's Disease." The comprehensive IDEAS study was not approved by CMS until March 2015 and recruitment did not start until February 2016, nearly two and a half years after the Decision Memorandum, during which time beta amyloid PET was not available to Medicare beneficiaries.

More than eight years later, despite the completion of the largest imaging trial and largest Alzheimer's trial in history (the IDEAS study), enrolling over 18,000 participants, the CED restriction has not been removed. This has resulted in substantial access barriers to beta amyloid PET imaging to this day. CMS has not acted on the September 2020 request for reconsideration of the September 2013 Decision Memorandum. Given our experiences with the beta amyloid PET CED, MITA is concerned that a CED restriction directed against amyloid targeted therapies will result in limited and delayed access to current and future Medicare beneficiaries.

III. Imposition of Class-Wide CED for Anti-Amyloid mABs Is Inappropriate

MITA is particularly concerned that the agency is proposing to restrict coverage for the **entire class** of FDA approved mABs directed against amyloid for the treatment of Alzheimer's disease to coverage in a RCT under CED. Only a single drug in this class has been approved by the FDA at this time.

MITA believes that it is impermissible to predetermine that an entire class of therapies that may be reviewed by the FDA in the future is not reasonable and necessary outside of CED, based on an evidence review focused on a single FDA-approved product. Under chapter 13, section 13.5.4 of the Medicare Program Integrity Manual, whether an item or service is reasonable and necessary is determined, in part, by whether it "meets, but does not exceed, the patient's medical need" and is "at least as beneficial as an existing and available medically appropriate alternative." These factors may differ depending on the individual product.

Furthermore, CED study requirements will likely duplicate ongoing Phase 3 studies conducted by companies on their individual therapies. This will hamper development and commercialization of future Alzheimer's therapies in unforeseeable ways. The establishment of stringent CED requirements for this class of mABs will chill innovation, undercutting promising advances in Alzheimer's treatment in direct opposition to NAPA's mandates.

CMS has not imposed CED on drugs in the past. CMS twice proposed and subsequently withdrew proposed CED requirements for CAR T therapies and for Next Generation Sequencing tests for advanced cancer. These examples presented similar breadth and unpredictability concerns to the imposition of a class-wide CED requirement for anti-amyloid mABs for treatment of Alzheimer's. In both historical cases, CMS elected not to finalize these proposed CEDs.

In the event that CMS does finalize CED for anti-amyloid mABs for treatment of Alzheimer's, it is critical that CMS provides explicit and clear articulation of how a compound could exit CED as well as the coverage pathways through and beyond CED with the delivery of positive clinical trial results. Adoption of a one-size-fits-all approach that treats different products within the class the same is inappropriate.

IV. FDA-Approved Therapies for Alzheimer's Disease Should be Covered to Label

We note that CMS and the Medicare Administrative Contractors (MACs) have a longstanding policy of covering FDA-approved drugs and biologicals in accordance with their FDA label. This policy recognizes the two agencies' distinct spheres of responsibility – FDA to assess whether a therapy is safe and effective, and CMS to determine whether it is reasonable and necessary based on health outcomes.

We believe that a safe and effective Alzheimer's therapy should be reasonable and necessary for beneficiaries suffering from Alzheimer's, given the lack of alternative treatment options. For CMS to limit

coverage for current and future FDA-approved drug and biological products, based on the same evaluation factors as the FDA, undercuts the role of FDA and creates a precedent that will promote provider and beneficiary uncertainty as to whether they will be permitted to access FDA-approved drugs.

Moreover, CMS' proposal to adopt a substantially more restrictive coverage policy for the first FDA-approved Alzheimer's therapy in two decades than it does for most newly FDA-approved drugs is not consistent with Congress' requirement, under NAPA, that HHS "accelerate the development of treatments that would prevent, halt, or reverse the course of Alzheimer's." Instead, CMS is proposing to essentially deny access to such a treatment, after it has been FDA approved.

V. Conclusion

We appreciate CMS' review of these comments and its careful consideration of the views of stakeholders in developing this important NCD. MITA believes CMS' final decision should provide beneficiary access to both coverage of mABs directed against amyloid for the treatment of Alzheimer's disease and beta amyloid PET both inside and outside CED. We count on your careful positive consideration of our requests on this important matter. If you have any questions, please contact Sue Bunning at 703-340-4100 or by email at sbunning@medicalimaging.org.

Sincerely,

Patrick Hope
Executive Director, MITA

MITA is the collective voice of medical imaging equipment, radiopharmaceutical manufacturers, contrast agent innovators and product developers. It represents companies whose sales comprise more than 90 percent of the global market for medical imaging technology. These technologies include: magnetic resonance imaging (MRI), medical X-Ray equipment, computed tomography (CT) scanners, ultrasound, nuclear imaging, radiopharmaceuticals, contrast agents and imaging information systems. Advancements in medical imaging are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. The industry is extremely important to American healthcare and noted for its continual drive for innovation, fast-as-possible product introduction cycles, complex technologies, and multifaceted supply chains. Individually and collectively, these attributes result in unique concerns as the industry strives toward the goal of providing patients with the safest, most advanced medical imaging currently available.