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EANM Reply to EMA Concept paper on the need for revision of the guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease

Alzheimer's disease (AD) is neuropathologically characterized by extracellular deposition of amyloid β (Aβ) plaques associated with downstream neurodegenerative processes.
With the emergence of disease-modifying anti-amyloid monoclonal antibodies, including lecanemab and donanemab, biomarkers are now integral to regulatory trial design, patient selection, treatment monitoring, and treatment duration decisions.
Positron emission tomography (PET) imaging enables in vivo visualization and quantification of cerebral amyloid pathology and provides direct information on amyloid burden, with established relevance for diagnosis, patient stratification, therapeutic monitoring, and treatment duration assessment. Among available biomarkers, PET imaging currently represents the only modality capable of direct in vivo measure of cerebral amyloid plaque burden. Indeed, while fluid biomarkers are increasingly relevant for screening and early detection, and structural MRI remains indispensable for safety monitoring and assessment of neurodegeneration, these modalities should not be positioned as alternatives to PET. Rather, they provide complementary and non-interchangeable biological and clinical information.

MRI plays a central role in the detection of amyloid-related imaging abnormalities (ARIA), whether spontaneous or treatment-related, as well as in the evaluation of cerebrovascular comorbidities and structural disease staging. In contrast, PET uniquely enables the direct in vivo quantification of the amyloid burden and pharmacodynamic treatment effects. Imaging modality selection should therefore be guided by the specific clinical and regulatory objective - including diagnostic confirmation, safety surveillance, target engagement assessment, treatment response monitoring, and treatment discontinuation decision-making. In this framework, PET imaging should have a unique and non-substitutable role within both clinical development and therapeutic implementation pathways, and its integration should be reflected accordingly in revised regulatory guidance.

Amyloid and Tau PET

Three amyloid PET tracers are authorized in Europe and are widely available across clinical and research centres. Standardized frameworks for visual interpretation and quantitative reporting are established and continue to evolve, supporting harmonized use across multicentre trials.
Tau PET reflects downstream neurodegenerative pathology and provides spatially resolved assessment of disease stage more closely aligned with clinical impairment than amyloid alone.

Patient Selection for Treatment

The presence of cerebral amyloid pathology is a mandatory inclusion criterion in all pivotal clinical trials of anti-amyloid monoclonal antibodies and is expected to remain essential in clinical implementation. This requirement can currently be fulfilled using either fluid biomarkers (CSF or plasma) or amyloid PET imaging.

Fluid biomarkers offer high sensitivity, scalability, and cost efficiency and are therefore well suited for large-scale screening. However, amyloid PET provides spatially resolved and quantitative information that cannot be obtained from indirect fluid measures. As the only direct in vivo measure of cerebral

amyloid plaque burden, amyloid PET offers high diagnostic specificity, particularly in borderline or discordant cases, and remains critical prior to treatment initiation.

Recent evidence supports cost-effective biomarker algorithms in which fluid biomarkers are used for initial screening, with amyloid PET reserved for individuals with intermediate or inconclusive fluid results. Nevertheless, in the context of treatment initiation, a baseline amyloid PET scan is strongly recommended to:

- Facilitate interpretation of amyloid clearance (complete, partial, or absent)
- Inform scheduling and interpretation of follow-up PET assessments
- Assess regional amyloid distribution, including occipital involvement associated with increased ARIA risk.

Furthermore, Tau PET distribution correlates with Braak staging and cognitive status, supporting its role as an in vivo staging biomarker. Evidence supporting fluid biomarkers for late-stage disease stratification remains limited, and tau PET currently represents the most direct modality for biological staging. Post hoc analyses from anti amyloid therapy trials indicate that individuals with lower baseline tau burden derive greater clinical benefit, suggesting a predictive enrichment role. Additional trial independent data further support the prognostic value of tau biomarkers.

Establishing a robust imaging baseline is also essential to enable longitudinal interpretation of treatment response and to support evidence generation for downstream regulatory and health technology assessment (HTA) evaluations.

From a regulatory implementation perspective, biomarker requirements must remain aligned with European infrastructure readiness. Capacity analyses conducted within the European nuclear medicine community indicate that amyloid PET availability could increase substantially in the presence of reimbursement. Furthermore, real-world treatment uptake projections suggest that only a minority of diagnosed patients will ultimately receive anti-amyloid therapy, indicating that baseline PET imaging for all eligible patients is operationally feasible.

Beyond scanner capacity, equitable and scalable deployment of amyloid PET across Europe requires coordinated implementation strategies grounded in harmonization and quality assurance.
This includes standardized acquisition protocols, cross-center quantitative performance standards, and accreditation frameworks such as those developed within the EARL (EANM Research Ltd.) program. EARL accreditation provides validated harmonization of quantitative PET measures across tracers, scanners, and institutions, thereby ensuring reproducibility, inter-site comparability, and regulatory-grade analytical robustness in both clinical trials and clinical practice.

Standardization must also encompass structured reader training, certification of interpreting physicians, and accreditation of imaging centers. In parallel, controlled reference databases are required to evaluate and validate image quantification software tools, ensuring cross-platform comparability and regulatory qualification of quantitative outputs.

Integration of amyloid/Tau PET within biomarker-guided care pathways will further require alignment with fluid biomarker pre-screening strategies and the establishment of sustainable reimbursement frameworks. Coordinated alignment between regulatory guidance, professional society standards, and implementation infrastructures will therefore be critical to ensure operational feasibility and equitable access across EU Member States.

Clinical Trial Endpoints

Amyloid PET has served as a key secondary and supportive endpoint in all pivotal anti-amyloid therapy trials. These studies demonstrated dose-dependent and quantifiable reductions in amyloid plaque burden with clear separation from placebo.

PET endpoints provide direct molecular evidence of disease-modifying activity and remain unmatched by fluid biomarkers, which primarily reflect peptide dynamics rather than absolute plaque burden. Both visual assessment and quantitative metrics should be jointly considered in endpoint evaluation.
Broader incorporation of standardized PET endpoints within regulatory trial designs would enable generation of datasets suitable not only for regulatory approval but also for post-hoc health technology assessment analyses. Such datasets would support evidence-based optimization of imaging utilization, patient selection, treatment sequencing, and therapeutic positioning within healthcare systems.
Experience from other high-cost therapeutic domains has demonstrated that when molecular imaging is included only as an exploratory or optional endpoint, resulting datasets may be insufficiently structured for HTA evaluation. This limitation can constrain assessment of comparative effectiveness, cost-effectiveness, and optimal clinical positioning of therapies.
In particular, the absence of harmonized baseline and longitudinal imaging acquisition may preclude robust evaluation of target engagement dynamics, treatment response heterogeneity, and imaging-guided treatment discontinuation strategies, parameters of direct relevance to payer and reimbursement decision-making.

Prospective integration of mandatory, standardized PET endpoints within trial protocols would therefore ensure that regulatory efficacy evaluation and HTA evidence requirements are aligned from the outset, reducing the need for post-hoc methodological reconstruction and facilitating more efficient access pathways following authorization.

Treatment Response Monitoring

Amyloid PET functions as a pharmacodynamic biomarker by directly demonstrating biological treatment effects within the brain. It enables quantification of residual amyloid burden during and after therapy.
Fluid biomarkers are not suited to evaluate treatment effects, as these largely reflect amyloid mobilization and clearance into CSF or plasma rather than remaining cerebral plaque burden.
PET and fluid biomarkers should therefore be viewed as complementary modalities providing distinct biological information.
Systematic acquisition of longitudinal PET data during follow-up remains limited in current trials and represents a critical evidence gap for both clinical and HTA decision-making.

Treatment Duration and Stopping Decisions

Amyloid PET has played a central role in treatment duration decision frameworks within clinical trials. Therapy discontinuation based on predefined Centiloid thresholds demonstrates the utility of PET in determining when sufficient amyloid clearance has been achieved. Only PET imaging can establish whether cerebral amyloid pathology has been adequately removed to justify treatment cessation. This approach carries significant health economic implications, as rational treatment discontinuation represents the most cost-effective strategy when high-cost disease-modifying therapies are employed.

Robust longitudinal PET datasets are therefore essential to support evidence-based stopping rules. Trials in which imaging acquisition is limited, or non-mandatory restrict the feasibility of post-authorization HTA and payer decision-making.

Experience from other high-cost therapeutic areas, including radioligand therapies, has demonstrated that regulatory trials not designed to generate HTA-relevant imaging evidence can result in substantial downstream uncertainty regarding optimal patient selection, treatment duration, and cost-effectiveness evaluation. Reliance on post-hoc analyses of datasets not originally structured for health economic assessment has proven methodologically challenging and has complicated reimbursement and access decisions across European health systems.

Avoiding similar evidence gaps in disease-modifying Alzheimer's therapies will require prospective integration of standardized, longitudinal PET imaging within trial designs, ensuring that both regulatory approval and HTA evidence needs are addressed in parallel.

The implementation of disease-modifying Alzheimer's therapies falls within the scope of the European Union Health Technology Assessment Regulation, under which Joint Clinical Assessments (JCAs) will increasingly rely on evidence generated during pivotal trials.
Alignment between regulatory evidence requirements and HTA evidence needs is therefore essential. Imaging biomarkers, particularly amyloid PET, provide direct measures of target engagement, treatment response, and biological disease modification, all of which are parameters of relevance to both regulatory benefit–risk evaluation and HTA comparative effectiveness assessment. Prospective incorporation of harmonized imaging endpoints, standardized acquisition protocols, and longitudinal follow-up assessments would enable datasets generated during regulatory development to be directly usable within HTA frameworks, minimizing duplication of evidence generation and accelerating patient access following authorization. Early dialogue mechanisms between regulators, HTA bodies, and trial sponsors, including joint scientific advice procedures should therefore encourage integrated imaging evidence strategies that satisfy both regulatory and payer evidentiary standards.

Conclusions and Regulatory Recommendations

Amyloid/Tau PET should remain an integral component of clinical trial design for disease-modifying Alzheimer's therapies.

Amyloid PET is essential for:

- Confirmation of treatment eligibility
- Quantification of target engagement
- Monitoring of pharmacodynamic response
- Determination of treatment duration and stopping thresholds

Revised regulatory guidance should:

- Recognize PET biomarkers as direct measures of cerebral pathology
- Support their use as trial endpoints and longitudinal monitoring tools
- Encourage mandatory baseline and follow-up imaging acquisition to enable HTA-relevant evidence generation
- Promote harmonization of acquisition and quantification standards
- Encourage alignment with European implementation frameworks to ensure equitable access

Proposed Clinical Biomarker Pathway

Implementation of structured biomarker pathways incorporating standardized PET acquisition and longitudinal follow-up will be essential not only for clinical decision-making but also for generating evidence suitable for Joint Clinical Assessments under the EU HTA Regulation.

Here we propose the following pathway which reflects a complementary biomarker strategy integrating scalable screening tools with definitive molecular imaging confirmation and monitoring:

1. **Screening and diagnostic support using fluid biomarkers**
   Plasma and/or CSF biomarkers serve as first-line screening tools due to scalability and cost efficiency.

2. **If amyloid fluid biomarkers are negative:**
   No further amyloid-specific testing is required.

3. **If amyloid biomarkers are positive:**
   Proceed to treatment eligibility assessment, including:
   - MRI safety screening (ARIA risk, cerebrovascular disease)
   - Genetic risk profiling where applicable
   - Clinical staging and comorbidity evaluation

4. **Baseline amyloid PET prior to treatment initiation**
   Recommended to:
   - Confirm cerebral amyloid burden
   - Establish quantitative baseline for treatment monitoring
   - Support longitudinal pharmacodynamic interpretation
   - Inform treatment duration planning
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5. **Longitudinal amyloid PET follow-up (trial and post-authorization settings)**
   Enables:
   - Assessment of treatment response
   - Evaluation of amyloid clearance dynamics
   - Evidence-based treatment discontinuation decisions
   - Generation of HTA-relevant longitudinal datasets

Coordinated collaboration between regulators, HTA bodies, clinical societies, and healthcare systems will be essential to ensure that biomarker requirements remain scientifically robust, operationally feasible, and economically evaluable across the European Union.