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RE: [Docket No. FDA-2013-D-0077] "Early Alzheimer's Disease: Developing Drugs for Treatment; Draft Guidance for Industry; Availability."

Dear Dr. Buracchio,

We appreciate the opportunity to comment on the March 2024 revised draft "Guidance for Industry on Early Alzheimer's Disease: Developing Drugs for Treatment." We would like to thank you for issuing this guidance to clarify ways to address emerging developments in a challenging disease space, where recent promising treatments have focused on interventions in the early stages of the disease to slow progression.

- Our organizations support a biological rather than a syndromic definition of disease, especially in the context of clinical trials measuring the prevention, delay, or slowing of disease in early stages before dementia is clinically present. We also support applying time-to-event analyses to provide a clear indicator into the efficacy of intervention efforts in clinical trials.

- While the focus of the guidance is on early-stage Alzheimer's disease, it would be beneficial for the FDA to provide guidance on studies with patient populations in later Stage 3 and into Stage 4 given that many people experience fluidity across staging lines (as noted in lines 121-122). We propose Stage 4 should be included in the scope of this guidance with similar outcome measure expectations as Stage 3, and for the FDA to further clarify and define when functional decline in Stage 3

constitutes a transition to Stage 4. Patients in Stage 3 or Stage 4 can be difficult to differentiate clinically, particularly in research populations using cognitive or functional measure. The overlap between these populations is underscored by ongoing research combining both Stage 3 and Stage 4 patients. As such, within a study, a common primary outcome should be applied to the entire population.

- We note the addition in lines 96-98 of "cognitive symptoms reported by patients or observers." Does this imply that Patient Reported Outcomes data is acceptable for use in determinations of inclusion criteria for trials in early AD?

- We request further clarification in the revision in lines 135-136 "that biomarker evidence of disease will establish the reliable diagnosis of subjects in trials of early AD." While this clarification may help better identify individuals experiencing very early-stage disease where intervention can occur prior to functional loss and decrease the enrollment of patients without Alzheimer's disease who then have to be dropped from the trial at a later date, the draft's current construction could be misinterpreted as guidance for clinical diagnosis, rather than solely for clinical trials.

- The draft guidance states "Both clinical outcome assessments and biomarkers should be included in clinical trials enrolling subjects with AD Stages 1-3; however, the approval pathway may differ based on the selection of the primary endpoint and its ability to measure a clinically meaningful change. Direct measures of clinical benefit or validated surrogate endpoints may support a traditional approval. Surrogate endpoints or intermediate clinical endpoints that do not directly measure clinical benefit but that are considered reasonably likely to predict clinical benefit may support an accelerated approval (see section IV. C.). Under the accelerated approval pathway, post-approval trials have been required to verify and describe clinical benefit." We request that the FDA clarify how this would affect Stage 1 trials (i.e., is validation the only way to approval for those, since clearly no clinical impact is measurable at that stage, and post-approval trials for Stage 1 could take many years for people to transition to Stage 2 while still having no detectable functional impairment). This will be increasingly important for targeted research on populations with the greatest risk of disease, including those with genetically determined disease (Dominantly Inherited Alzheimer's Disease, APOE-4 homozygotes, Down syndrome). Line 263 states that "an effect on various biomarkers, may be an appropriate measure." Can the agency provide any additional information as to what would constitute validation for these biomarkers?

- We support the draft language, "A surrogate endpoint that is determined to be appropriate for use in a particular therapeutic clinical development program should not be assumed to be appropriate for use with a different product or trial population." But we are concerned that disparities may be observed on standard neuropsychological tests, such as for race, ethnicity, or neuroatypical persons, even when matched for education. Therefore, use of "sensitive neuropsychological measures" in the draft guidance would benefit from FDA providing additional language explaining its expectations about the accuracy of such measures across diverse populations.

- We encourage FDA to validate diagnostic algorithms and set the expectation that biomarker data must allow for measurement for potential differences in how the biomarkers are expressed among disparate populations (including, but not limited to age, biological sex, and neurodivergence).

- We also encourage data collection to include information relevant to social determinants of health that may have a material impact on the development, progression, or intensity of Alzheimer's disease.[1]

- We urge FDA not to use of terms such as "Target", "Subpopulations" and "Subjects", that are offensive to certain populations. Revisions to language in the guidance that instead address disproportionately impacted, under-engaged, or underrepresented populations may be instructive for sponsors attempting to enroll more representative populations in clinical trials.

- Does the FDA have a preferred approach to reducing disparities in testing, clinical endpoints, or outcomes that could be addressed in the draft guidance?

We applaud FDA for its leadership in issuing guidance that will catalyze more effective drug development for earlier treatment of Alzheimer's. Thank you for your careful consideration of our comments. Any questions on our comments can be directed to Beth Mathews-Bradshaw at bmbradshaw@agingresearch.org or Ian Kremer at ikremer@leadcoalition.org.

[1] Adkins-Jackson, Paris B., et al. The Structure and Social Determinants of Alzheimer's Disease Related Dementias. Alzheimer's & Dementia. 19 Apr 2023. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.13027