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Rethinking FDA's 2013 Guidance on Developing Drugs for Early Stage Alzheimer Disease

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The FDA's draft guidelines for developing drugs for early stage Alzheimer disease¹ both advance a number of issues for Alzheimer therapeutics and create some challenges. The guidelines advance regulatory support for new research diagnostic criteria,^{2,3} and for biomarkers to enrich trials with participants who have amyloid pathology. They clarify that currently proposed biomarkers are not surrogate markers for clinical outcomes, and those that would be used to support disease modification claims must reflect the progression of the underlying Alzheimer pathology. Indeed, they put the prospects for disease modification marketing claims in realistic context by emphasizing that they are extraordinary, major claims implying that nearly everybody at risk for AD would need to take the proposed medication.⁴

Yet, other guidance on preclinical Alzheimer disease, mild cognitive impairment due to Alzheimer disease (MCI due to AD or prodromal AD), and recommendations for clinical outcomes in drug development are challenging and need to be fixed.

Preclinical Alzheimer disease and accelerated approval

The FDA describes preclinical AD as "subtle cognitive deficits [that] may be evident only through the use of sensitive measures of neuropsychological performance." Sponsors may gain accelerated or provisional approval for a drug for preclinical AD by using one cognitive assessment procedure as the sole, primary efficacy measure in a pivotal clinical trial. The rationale, however, is that the cognitive effect would be reasonably likely to predict clinical benefit. A sponsor would then be required to demonstrate clinically meaningful effects in post-marketing studies.¹

Identifying people with *preclinical* AD should require evidence for the presence of Alzheimer pathology and knowledge that the diagnosis will predict subsequent *clinical* Alzheimer disease. Subtle cognitive worsening or deficits in older individuals are not necessarily related to amyloid or Alzheimer pathology, but may be related to age-associated cognitive decline, cerebrovascular changes, trauma, TDP43 or synucleins proteinopathy, medical illness, medications, or other conditions. Many older individuals who score in lower ranges of neuropsychological test scores may show Alzheimer disease pathology but not go on to develop MCI or AD.⁵

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If a preclinical AD diagnostic construct is not validated, then relying on cognitive assessments as a sole, primary efficacy measures for drug approval risks approving drugs for various and ill-defined conditions that do not progress to clinical AD in any reasonable timeframe. For example, one can hypothesize cholinesterase inhibitors, cognitive enhancers, neuronal nicotine receptor modulators, memantine, or drugs that may attenuate the synaptic effects of soluble amyloid-beta, may have longer-term, measurable cognitive effects for preclinical trials participants. The effect, however, may be in those who progress to clinical AD, do not progress to clinical AD, or do not have Alzheimer pathology *per se*. Although salutary cognitive outcomes from safe drugs would be welcomed, the outcomes would not necessarily indicate a treatment specific to Alzheimer disease or predict long-term benefit.

The FDA might better describe its requirements for validating the range of preclinical Alzheimer disease diagnoses, the risk rates for subsequent clinical AD that would be required, and its view on the kinds of drugs that would be appropriate for preclinical AD under its accelerated approval process. Further, the FDA might expand their draft guidelines to include pathways for the development of drugs for age-associated memory impairment, age-associated cognitive decline, and the early manifestations of TDP43 and synucleins proteinopathies as these are common comorbid conditions and may need to be distinguished from preclinical AD.

Participants in preclinical AD trials are, on average, unlikely to decline substantially during a trial of even several years duration. Many volunteers would improve on test scores due to the ebb and flow of their preclinical condition, measurement error, misspecification, and misdiagnosis. In this scenario, an otherwise effective test drug will likely not be able to show statistical significance on a sole cognitive assessment unless the drug causes absolute improvement over baseline scores. These circumstances may show efficacy of drugs that have *cognitive enhancing, neurotropic, or neuroregenerative effects*. Conversely, drugs that attenuate only the progression of Alzheimer pathology (and do not reverse it) may fail to demonstrate detectable cognitive effects and consequently may halt further development.

In sum, the accelerated approval scenario appears to favor drugs with cognitive enhancing effects and assessed over relatively shorter treatment durations. For postulated disease-modifying drugs without symptomatic effects, much larger samples and longer follow-up periods would be required such that cognitive worsening could be detected in sufficient numbers that potentially a drug effect could be observed.

MCI due to AD/prodromal AD and outcomes guidance

The guidelines correctly recognize that MCI due to AD or prodromal AD is incipient Alzheimer disease dementia and substantially the same diagnosis. According to the NIA - Alzheimer's Association criteria on which the FDA relies, MCI due to AD is defined by concern about cognitive decline, objective evidence of progressive cognitive impairment (nearly always memory), "preservation of independence in functional activities," and not meeting criteria for dementia.²

The threshold for memory impairment required for the diagnosis of MCI due to AD,² for entry into several earlier MCI clinical trials,⁶ and the Alzheimer's Disease Neuroimaging Initiative⁷ is the same as is typically required for an Alzheimer disease dementia diagnosis. Moreover, there is virtual equivalence and substantial overlap in clinical and biomarker values between the more cognitively impaired half of MCI due to AD patients and the less impaired half of the AD patients in the ADNI.⁸ National Alzheimer's Coordinating Center data from the NIH-funded Alzheimer disease centers similarly show that over 92% of

individuals diagnosed with mild or very mild AD would fulfill criteria for MCI due to AD as well.⁹

The requirement for “preservation of independence in functional activities” is complicated as,

“Persons with MCI commonly have *mild problems performing complex functional tasks* which they used to perform previously, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors at performing such activities than in the past. Nevertheless, they generally maintain their *independence of function in daily life*, with minimal aids or assistance.”² [Italics added]

“There is generally mild functional impairment for complex tasks, but basic activities of daily living should be preserved, and the person should not meet criteria for dementia.”²

The NIA - Alzheimer’s Association workgroup on dementia due to Alzheimer disease further explains,

“[T]he differentiation of dementia from MCI rests on the determination of whether or not there is *significant interference in the ability to function at work or in usual daily activities*. This is inherently a *clinical judgment made by a skilled clinician* on the basis of the individual circumstances of the patient and the description of daily affairs of the patient obtained from the patient and from a knowledgeable informant.”¹⁰ [Italics added]

Thus, the distinction between MCI due to AD and dementia due to AD hinges on the judgment of a skilled clinician on whether or not “mild problems performing complex functional tasks” represents “significant interference in the ability to function at work or in usual daily activities.” The distinction is critical, arbitrary, and depends on the sources of information available to the clinician, patient-related and environmental factors such as age, education, occupation, living situation, and culture, and the perception of informants and the patient.

In sum, patients diagnosed as MCI due to AD have considerable cognitive impairment, mild functional impairment, and most could have been diagnosed as Alzheimer disease dementia. Conversely, others diagnosed as mild Alzheimer disease could have been diagnosed as MCI due to AD. As described previously, the diagnosis of MCI due to AD – and especially when accompanied by positive amyloid biomarkers – impinges on or compromises the diagnosis of Alzheimer disease dementia.⁹ The principles and guidelines for drug development for MCI due to AD should not be different from those for Alzheimer disease.

A composite scale for MCI due to AD?

The FDA should maintain its current guidance and require a co-primary outcomes approach for demonstrating efficacy in MCI due to AD or prodromal AD precisely because of its overlap with AD. It should not recommend that a combined or composite scale be used as a sole primary efficacy outcome to support a regulatory claim unless it requires that the cognitive and functional components of such a combined scale are analyzed separately and can be shown to be individually meaningful. As progressive cognitive impairment is a defining criterion for MCI due to AD, an effective drug for people with MCI due to AD must show at least a clear cognitive effect, and further demonstrate overall “global” efficacy or improvement of function. Otherwise, any clinical meaning inferred from only a composite rating most likely will be of dubious value as the outcome could be driven by any one cognitive or functional component or very small effects from a few components.

The FDA's *specific suggestion*¹¹ that the Clinical Dementia Rating- Sum of Boxes (CDR-SB)¹² serve as the composite scale and sole primary outcome for MCI due to AD trials is misguided. The suggestion will be treated as a regulatory requirement by pharmaceutical companies, NIH, and academics. The FDA must operationalize the guidelines to describe the essential characteristics of composite scales for MCI trials.

A real risk and unintended consequence of FDA's *specific suggestion* is that the CDR-SB will be taken as the *de rigueur* measure of drug efficacy for prodromal AD trials in much the same way as the ADAS-cog has been used as the measure for cognitive improvement in Alzheimer disease trials despite its substantial clinical and metrical limitations. The use of the CDR-SB as the sole, primary outcome criterion will create a constrained standard, limit efforts to precisely assess the cognitive and functional effects of new drugs, and inhibit innovation in an area where evidence-based clinical research practices have not been established. The *de facto* definition of an effective drug for prodromal AD will be reduced to a drug that improves a CDR-SB score compared with placebo.

Already, several phase 2/3 trials use the CDR-SB as the sole primary outcome for MCI due to AD or prodromal AD. For example, a phase 2/3 trial for gantenerumab appears to comply with the draft guidelines (NCT01224106). The trial uses an episodic memory test and amyloid biomarker to define and enrich a prodromal AD clinical trials sample, the CDR-SB as the primary outcome, and the ADAS-cog and functional activities as secondary outcomes. Two plausible outcomes from such a trial may lead to substantial uncertainty: (1) the CDR-SB significantly favors the drug, but the ADAS-cog, functional or biomarker outcomes do not; or (2) the CDR-SB is not significant but the ADAS-cog, functional rating scales, or biomarkers favor the drug. Indeed, these scenarios have occurred in mild AD clinical trials. A tarenflurbil mild AD subgroup showed positive effects for the CDR-SB but not for the ADAS-cog;¹³ and a mild AD subgroup of the second solanezumab trial showed negative effects on the CDR-SB but positive effects on the ADAS-cog and ADLs. One might wonder how solanezumab's development program would have been affected if the trial had been done in MCI due to AD and the CDR-SB had been the sole primary outcome under the new FDA guidelines?

Summary and recommendations

The FDA draft guidelines encourage precise measurement for preclinical AD where diagnostic accuracy is less certain, but blunt measurement for MCI due to AD where diagnostic accuracy is more certain. The net effect is that the guidelines will likely make it harder – not easier as the New York Times editors worried – to show convincing effects for a drug for early-stage diagnoses and will cause other unintended consequences. For example, increased scrutiny of exactly how the CDR has been used in earlier trials will lead to changes in methods, interview approach, completion of worksheets, scoring or translating findings to box scores, video and audio monitoring, centralized ratings, and will effectively change the CDR's characteristics.

The FDA should revise its draft guidelines to affirm the principle of the co-primary outcomes approach (which notably could still allow the CDR as a co-primary outcome). The agency could better encourage the development of outcomes instruments for at-risk and early stage AD clinical trials rather than to prematurely recommend one or another approach. It is important to include outcomes that might be most responsive to a new drug. For example, it is quite possible that brief, direct tests of mental status, executive function, and instrumental activities may be better-suited, less biased, more accurate and precise at detecting relevant change due to a new drug than existing composite scales designed for disease staging and not necessarily for clinical trials. More should be done to develop the

definitions, application, and pragmatic validity of early stage AD diagnoses; but for drug development purposes they should be treated similarly with mild Alzheimer disease dementia.

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