A Review of FDA's Updated Guidance for Developing Drugs to Treat Early Alzheimer's Disease

There has been a renewed interest in clinical trials of drugs to treat early Alzheimer's disease (AD) owing partially to recent advances in the understanding of pathophysiological processes that occur well before the emergence of clinical symptoms, but also to the recent failures of trials of disease-modifying drugs aimed at later stages of the disease. The Food and Drug Administration (FDA) has responded to this by recently issuing draft guidance to assist sponsor companies in the development of drugs for the treatment of the stages of sporadic Alzheimer's disease (AD) that occur before the onset of overt dementia, collectively referred to as "early AD"[1]. This updated guidance outlines the FDA's current thinking regarding the selection of patients with early AD for entry into clinical trials, and the appropriate endpoints for clinical trials of these populations, and represents a major revision from former draft guidance issued in February 2013[2]. This review will highlight the more salient aspects of this guidance that may impact drug developers, and will make comparisons to prior FDA guidance as well as recently updated European guidance. Two major departures in thinking about early AD come in the new-found appreciation of changes in cognition as being meaningful in terms of clinical benefit in and of themselves, and with that a rejection of the long-held dichotomy of function and cognition in respect to demanding dual-outcome measures; and in the growing role that biomarkers have in both reflecting the pathophysiological changes in early stages of disease when there may be no discernible functional impairment nor cognitive abnormality, and as an indicator of drug activity and possible surrogate for clinical outcome.

Diagnosis of Early AD

The updated FDA guidance demands that enrolment in any efficacy trial in AD, including early AD, be based on consensus diagnostic criteria reflecting a contemporary understanding of the pathophysiology and evolution of AD with a focus on objective tests and, when appropriate, history and physical examination designed to determine the presence or likely presence of AD, and to exclude other conditions that can mimic AD. As these pathophysiological changes precede the development of clinical findings and progress on a continuum, the updated guidance reflects staged diagnostic criteria. This represents a major departure from previous FDA guidance which supported various sets of criteria related to the diagnosis of mild cognitive impairment (MCI), and particularly the amnestic subtype to help identify those patients who are most likely to progress to dementia, citing examples of both research criteria for *prodromal AD* published by the International Working Group for New Research Criteria for the Diagnosis of AD[3]; as well as for *MCI due to AD* by the National Institute on Aging – Alzheimer's Association working group[4]. Importantly, the updated guidance does not address any specific diagnostic frameworks such as these nor endorse any specific nomenclature, but rather categorises stages of early AD based on the presence of pathophysiological changes, neuropsychological abnormalities, and functional impairment as in the below table:

Stage 1	Patients with characteristic pathophysiologic changes of AD but no evidence of clinical impact.
Stage 2	Patients with characteristic pathophysiologic changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures, but no functional impairment.
Stage 3	Patients with characteristic pathophysiologic changes of AD, subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment.
Stage 4	Patients with overt dementia.

The updated guidance argues that is essential to accurately distinguish these four conceptual categories, even in the presence of a single continuous disease process in order to inform the selection of appropriate outcome measures. As such, drug developers must identify both the stage of AD defined for study eligibility as well as the stage of AD anticipated for the majority of the enrolled patient population at the time of primary outcome assessment for all proposed and completed studies, which may differ for studies of long duration. It is also fully expected that biomarkers will play a role in the identification of patients with early AD and the updated guidance speculates that it would be unusual to encounter a proposed clinical trial that does not include in the enrollment criteria some biomarker evidence of disease. The implications of demanding such biomarkers were reviewed in a prior article by the authors, who point out the practical issues related to the cost and burden to both sponsor companies and to subjects (and their caregivers) as well as the theoretical possibility of having an incomplete biomarker profile or some degree of discordance amongst biomarkers for patients making accurate classification problematic[5].

Outcome Measures

The updated guidance stresses that the outcome measures must be appropriate for the stage of illness and outlines several broad possibilities for each stage but interestingly does not name any single outcome measure. This represents a major departure from past guidance which suggested that patients with prodromal AD or MCI due to AD were likely to have relatively mild but noticeable impairments in their daily functioning, and therefore it was important to demonstrate that a drug favourably affects these deficits, in addition to showing an improvement in cognition and named the Clinical Dementia Rating scale, specifically the Clinical Dementia Rating – Sum of Boxes as an example of a suitable outcome measure; although open to others.

The proposed categories of outcome measures related to each stage of early AD are as follows:

Stage 1: The updated guidance submits that for Stage 1 patients, a clinically meaningful benefit cannot be measured as there is no clinical impairment to assess. As such an effect on various biomarkers alone may serve as a primary efficacy measure, and in principle serve as the basis for an accelerated approval should the biomarker effects be found to be reasonably likely to predict clinical benefit, with an appropriate post-approval requirement for confirmation. Of note, a pattern of treatment-related effects across multiple biomarkers would increase the persuasiveness of the putative effect.

Stage 2: The updated guidance opines that it may be difficult to establish a clinically meaningful effect on cognition in a reasonable period of time for Stage 2 patients where there is no functional impairment but subtle cognitive dysfunction. Nonetheless, the FDA will consider strongly justified arguments that a persuasive effect on neuropsychological performance may provide adequate support for a marketing approval if the magnitude of the effect is large or if a pattern of beneficial effects was demonstrated across multiple individual tests. Conversely, the persuasiveness of showing significance on a single cognitive test that is not supported by consistent findings on other tests would be less persuasive. Prior guidance advocated the use of an accelerated approval mechanism to consider an effect on an isolated cognitive measure based on a single primary efficacy measure for a marketing approval[2]. Notably, no single cognitive test or cognitive domain is mentioned in the updated guidance.

Any considerations in terms of magnitude or pattern of effect must also take into account the relationship between cognitive measures and biomarkers, as well as changes to the evolution of more severe cognitive deficits and functional impairment. Should the cognitive effects be judged as "inherently clinically meaningful" then approval is possible. However, should these cognitive effects be found to be reasonably likely to predict clinical benefit, then an accelerated approval is possible with an accompanying post-approval requirement for a separate study to confirm the predicted clinical benefit. Understandably, a discussion with the agency would be required early in the development process.

A pattern of beneficial cognitive effects can be established by comparing z-scores corresponding to each individual cognitive domain. Clinically significant effects would be those that approach a 0.5 z-score improvement, a cutoff that is generally acknowledged by clinicians to reflect true changes in cognition not due to variability or chance. This z-transformed data also permits a shape or profile analysis that can help determine if treatment differentially affects one cognitive domain versus another, or if all domains are affected equally [6].

Stage 3: Unlike prior stages, patients in Stage 3 may have mild but noticeable impairments in functioning and therefore the updated guidance suggests that although it is generally acceptable to include neuropsychological measures of unknown clinical meaningfulness, it is imperative to demonstrate improvements in functional deficits. Although no specific functional outcome measure is named, the updated guidance suggests that the outcome measure should be an integrated scale that adequately and meaningfully assesses both daily function and cognitive effects as a single primary efficacy outcome measure. The development of novel approaches to a truly integrated outcome measure using real-world measures such as ease of financial transactions and adequacy of social conversation are encouraged. Alternatively, independent measures of function and cognition can also be utilised to support a claim but once again, none are named.

Additional Assessments and Biomarkers

The updated guidance suggests that a time-to-event or survival analysis (such as the time to the occurrence of a clinically meaningful event or impairment of daily function) can be used as a primary efficacy measure in early AD trials. In the past, this type of analysis was typically seen in the context of later stage early AD patients that utilised time to conversion from MCI to AD as a primary outcome measure. It is difficult to argue against the meaningfulness of this outcome measure but it is recognised that some change in a specific function or a composite measure may prove to be more advantageous than any single dichotomous variable in terms of study duration and sample size. Notoriously, many prior studies using such dichotomous outcomes greatly overestimated MCI conversion rates to AD and therefore significantly underestimated study duration resulting in a number of long and costly failed trials.

The updated guidance acknowledges that it is challenging to provide supportive evidence that a drug has an established clinically meaningful benefit based solely on biomarker evidence, as biomarkers in AD are not well enough understood to provide strong evidence of a persistent effect on the course of AD. As such, there is no consensus as to which specific biomarkers are most appropriate to support clinical findings in early AD trials, and inadequate information on which to establish a hierarchy of biomarkers as secondary outcomes. This differs from prior guidance, which at least theoretically allowed for approval based on the use of a biomarker as a single primary surrogate efficacy measure considered under accelerated approval if the biomarker was likely to predict ultimate clinical benefit[2]. Prior guidance was also willing to consider the argument that a positive biomarker secondary outcome measure in combination with a positive finding on a primary clinical outcome measure may support a claim of disease modification in AD based, of course, on widespread agreement in the research community that the chosen biomarker reflects a pathophysiologic process that is fundamental to the underlying disease[2]. There is also no mention in the updated guidance that a comparison of the rate of change based on slopes between active treatment and control could provide support for a claim of disease modification. Rather, consistent with past guidance, the updated guidance continues to support the use of randomised-start or randomised-withdrawal trial design as the most convincing approach to demonstrating a persistent effect on disease course.

Comparisons to Revised EMA Guidance

In relation to the almost simultaneously released European Medicines Agency (EMA) guidance on the clinical investigation of medicines for the treatment of Alzheimer's disease, the updated FDA guidance on early AD differences differs with respect to several salient areas including disease nomenclature (with EMA embracing the terms prodromal AD/MCI due to AD and preclinical AD) and the acceptability of efficacy endpoints for these two populations. In preclinical AD, the population is essentially asymptomatic (as in FDA Stage 1) and the presence of AD pathology is measured by biomarkers (both Aβ and Tau markers). European regulators continue to remain open in regard to the diagnostic criteria for prodromal AD/MCI due to AD, instead suggesting that efforts be focused on detecting a homogeneous group of patients with a defined rate of progression to AD dementia[7]. Similar to FDA guidance which recognises that patients with later-stage early AD and patients with AD in the earliest stages of dementia may not differ significantly, EMA guidance also acknowledges that the clinical characteristics of patients with prodromal AD/MCI due to AD may overlap with those at the milder end of the AD dementia spectrum, with similar levels of cognitive impairment and biomarker levels. Thus, the selection of patients with early AD for long-term interventional trials should not be unnecessarily subdivided, and subjects with prodromal AD/MCI due to AD and mild AD may be studied together[7].

European guidance also acknowledges the challenges of having co-primary endpoints of cognition and function, due mainly to the limitations of currently available scales that may be prone to ceiling effects and recommend that sponsors demonstrate the clinical relevance of their results. EMA guidance also call for the use of more sensitive item scoring for MCI-specific scales and/

or investigating only those domains that have been shown to be consistently impaired in this population; as well as the use of composite scales that have a combined assessment of cognition and its impact on daily functioning as a single primary endpoint, provided that this does not hinder demonstration of the significant contribution of both domains to treatment effects. Further, EMA guidance recommends that measures of instrumental activities, executive functions and health-related quality of life be included as secondary endpoints[7].

Although novel outcome tools sensitive to small neuropsychological changes in Preclinical AD are currently being developed, the EMA concedes that there is no "gold standard" as yet for the assessment of treatment effects in this population. And unlike the updated guidance from the FDA, which suggests that time to the occurrence of a clinical meaningful event during the progressive course of AD (such as a meaningful impact of daily function) could serve an acceptable primary efficacy measure in clinical trials in early AD, the EMA supports the use of time to event analysis as a complementary measure in order to support the relevance of a chosen outcome measured. As the main goal of treatment in the at-risk population remains prevention of cognitive impairment, as no biomarker can yet be considered a valid surrogate endpoint, the event of interest must be of clear clinical importance such as onset of cognitive impairment. While US regulators have remained largely silent on issues surrounding primary prevention designs, previously citing very large sample sizes and following patients possibly until death, EMA guidance notes that prevention trials will likely require relatively large sample sizes and long study durations, typically of at least three years[7]. However, given the dearth of scientific information on prevention no firm recommendations are provided.

Reconciling the disparities between US and European guidance may be challenging for sponsor companies designing and conducting international clinical trials as part of a development programme being submitted to both FDA and European regulatory agencies simultaneously. Obviously some degree of harmonisation of clinical diagnostic criteria and acceptable outcomes is needed at a minimum, and the adoption of the updated FDA guidance would need to be aligned with the corresponding recent EMA guidance (and vice versa) in order to facilitate and expedite the potential approval of new drugs for early AD.

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Henry J. Riordan, PhD

Henry J. Riordan is the Executive Vice President of Medical and Scientific Affairs and Global Lead for Neuroscience at Worldwide Clinical Trials. Dr Riordan has been involved in the assessment, treatment and investigation of various CNS drugs and disorders in both industry and academia for the past 20 years. He has over 100 publications, including co-authoring two books focusing on innovative CNS clinical trials methodology.

Email: henry.riordan@worldwide.com

Natalia E. Drosopoulou, PhD

Natalia E. Drosopolou is the Executive Director of Project Management and Franchise Area Lead in Neuroscience at Worldwide Clinical Trials. She received her PhD in Biochemistry, specialised in Developmental Neurobiology from King's College of London. With over 19 years in the clinical research industry, Dr Drosopoulou's experience spans from small intricate Phase I studies to large global Phase III programmes with a special emphasis in AD trials.

Email: natalia.drosopoulou@worldwide.com