Is "pre-preclinical AD" helpful to the EU/US CTAD Task Force?

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In their article in the Journal of Prevention of Alzheimer’s Disease on “Platform Trials to Expedite Drug Development in Alzheimer’s Disease: A Report from the EU/US CTAD Task Force”, Aisen and colleagues [*1*] offer an important description of the latest developments of these trials which are “essential to ensure that the field builds on and moves past the previous disappointments that have plagued amyloid trials … by testing the predictive value of biomarker status and the surrogate value of biomarkers” (p. 311, ibid). But defending early platform trials and describing the individuals involved in them can be done without the concept of “pre-preclinical AD” defended by the authors (p. 309, ibid). There are four reasons why.

Firstly, there is already significant controversy surrounding *pre*clinical Alzheimer’s Disease and anti-amyloid strategies, so by adding another prefix (*pre-pre*clinical AD), the term risks alienating critics from meaningful dialogue around these important trials in an already divided community [*2*]. Secondly, the International Working Group has reiterated its position that “biomarker-positive cognitively unimpaired individuals should be considered only at-risk for progression to Alzheimer's disease” (p. 484, [*3*]). It could therefore be argued, with such reasoning, that “pre-preclinical Alzheimer’s Disease” simply means being at risk of being at risk of developing dementia, and can lead to confusion. Thirdly, patients and their families are concerned by such labels, and for all the research community’s talk of a continuum, the lay conception of Alzheimer’s Disease is still that of an irreversible death sentence [*4*]. Thus, framing and communicating such a label with its normative connotations (i.e. of a current or impending disease state), could cause needless harm. Finally, there are neutral alternatives, including “cognitively unimpaired individuals with a low burden of Aβ pathology” as proposed by researchers who have made meticulous

efforts to define different thresholds at different levels of Aβ and other pathologies, measured with different methodologies [*5*].

Thus, promoting these valuable trials may be made unnecessarily harder by the use of the label “pre-preclinical AD” and the EU/US CTAD Task Force’s efforts might therefore benefit from dropping it.

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