Authors' reply

We thank Jonathan M Schott and colleagues for their correspondence on our Comment.[1] We agree that, ideally, a continuous outcome measure would be a preferable endpoint in a clinical trial compared with the discrete surrogate marker that we discuss in the Comment. We believe that a combination of continuous outcome measures and discrete clinical state scores (ie, a composite endpoint) would increase statistical power in a clinical trial relative to any single endpoint alone, given high within-patient and between-patient variability in both types of measures. The clinical trial simulator for Alzheimer's disease was built in its current format for three reasons.

First, in the clinical trials that have been unsuccessful to date, nearly all used a clinical marker of cognitive state as an endpoint. Longitudinal epidemiological analyses[2] have shown that a single continuous outcome measure, such as biomarkers, is subject to a great deal of within-patient and between-patient variability. We have done further analyses of the use of single measures (either discrete or continuous), or a combination of measures (drawn from clinical cognitive scores, brain scan-based measures, and biomarkers) as endpoints for clinical trials, and these analyses show similar conclusions to the results published in our Comment.[1] They again show that high within-patient and between-patient variability can mask the true treatment efficacy in a clinical trial, even if the treatment efficacy is high (>60%).

Second, we acknowledge the disadvantages of categorising continuous variables into discrete, clinically defined cognitive states.

However, at present, a clear understanding of precisely how well changes in biomarker concentrations reflect progression in Alzheimer's disease is not available.[3] We also acknowledge that the rate of transitions of patients from mild cognitive impairment to Alzheimer's disease, per year, is small in the existing databases on longitudinal cohort studies of dementia progression. The need for large and improved longitudinal studies of the progression to Alzheimer's disease is clear, with recruitment based on the rates of change of markers of disease that are sensitive to slight change over time in the preclinical stage of the disease, starting a decade or more before clinical symptoms of dementia typically become apparent. At present, the choice of a probability measure of individuals transitioning between clinical cognitive states is, to a large extent, dictated by the absence of a better understanding of longitudinal changes in biomarker measures within and between patients and associated measurement errors.[3] The US Food and Drug Administration has released a guideline for industry for the development of treatments for Alzheimer's disease, which suggests biomarkers should become more of a focus, but it stresses that a deeper understanding of the trajectory of the biomarkers over time is needed to determine progression to disease.[4]

Finally, we would like to draw the readers' attention to the power and usefulness of computer simulations, and how they can facilitate progress in clinical and drug development research on Alzheimer's disease. With clearly defined assumptions, quantitative data on longitudinal trends of a given endpoint choice (in a reasonable sample of patients), and an understanding of measurement error, such simulations can provide insights how best to detect signals of treatment efficacy in a clinical trial,

before the initiation of expensive phase 3 clinical trials. Trial simulators facilitate systematic quantitative analyses of different clinical trial designs, different endpoint choices, and different patient inclusion criteria.

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3 Hadjichrysanthou C, Ower AK, de Wolf F, Anderson RM, Alzheimer's Disease Neuroimaging Initiative. The development of a stochastic mathematical model of Alzheimer's disease to help improve the design of clinical trials of potential treatments. *PLoS One* 2018; **13:** e0190615.

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