

REPLY

Reply to Commentary by Cummings (2022): Surrogate endpoints extend beyond biomarkers

We thank Dr. Cummings for his support of the development of the SPIRIT/CONSORT-SURROGATE extensions and his correction that the primary outcome of the aducanumab trials in early Alzheimer's disease is the Clinical Dementia Rating-Sum of Boxes (CDR-SB) rather than the biomarker of magnetic resonance imaging-assessed amyloid load. However, this reply gives us the opportunity to clarify that the concept of surrogate endpoints in trials extends beyond biomarkers and includes intermediate outcomes.¹ Unlike biomarkers, intermediate outcomes can be directly perceived and be valued by trial participants but are intended as a substitute and predictor for a more distal patient-relevant final outcome. Whether an intermediate outcome should be considered a patient-relevant final outcome or surrogate endpoint depends on the aims of a trial and how that trial informs health-care policy.² A key question for regulators, payers, health-care professionals, and patients for the assessment of new treatments in this field is whether intermediate outcomes such as CDR-SB or Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) should be valued as final outcomes in their own right or, rather, as surrogate endpoints for the more severe disease progression, including residential care facility admission and/or premature death. If the latter, validation is required that the treatment-related improvements in CDR-SB seen in recent trials is strongly associated with an improvement in these more distal outcomes.³

We hope the completed SPIRIT-SURROGATE and CONSORT-SURROGATE checklists will clarify definitions of surrogate endpoints and guide trialists in improving transparency and completeness in their reporting.

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CONFLICTS OF INTEREST

The authors declare no conflicts. [Author disclosures](#) are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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