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Consider the source: the implications of informant type on outcome assessments

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Dear Dr. DeCarli,

In essentially every Alzheimer's disease clinical trial, a person with knowledge of the patient, usually the primary caregiver, serves as a proxy source of information. Validated informant-based instruments measure cognition, function, behaviors, and quality of life.

In "Errors in self-reports of health services use: impact on Alzheimer disease clinical trial designs," Chris Callahan and co-authors described the accuracy of informants' reports on yet another type of information: resource utilization by patients with Alzheimer's disease.¹ Their analyses of a subset of data from a randomized controlled trial of a coordinated care model, which successfully enrolled a real world sample of 173 patients with Alzheimer's disease,² found poor agreement between informant reports and objective healthcare utilization data. Informants most often underreported resource utilization. Modeling the impact of this poor agreement on statistical power shows that trials that use informant-based resource utilization outcomes, compared to trials using objective data, will need to increase their sample sizes by as many as 150 patients per arm.

The authors acknowledged limitations of their study, including the lack of private payer and self-pay utilization data and that the cost of assembling the objective dataset, even without private payer information, may outweigh the cost associated with simply increasing trial sample sizes. One additional limitation should be noted as well, a limitation that could have important implications to planning future clinical trials.

The subanalysis included 100 subjects, selected because of their enrollment at an urban safety net health system. This selection may have resulted in an important sample bias. In the original trial, 42% of the cohort was composed of spousal dyads, but in the current study the sample included only 17 spousal dyads (17%).

Why does this matter? Several studies suggest that relationship to the patient may be associated with bias in informant-based outcomes reporting. Non-spousal informants are, for example, more likely to provide discrepant measures of memory,^{3,4} orientation,³ and problem solving³ and are also more likely to be replaced during the study⁵ or dropout prior to its completion.⁶ Each of these can increase variance. The inclusion of a preponderance of

nonspousal informants from the original trial may have therefore inflated the discrepancy observed between informant report and objective data, relative to the entire original trial sample or, even more so, compared to most Alzheimer's disease clinical trials where spousal caregivers predominate.⁶

Enrollment of underrepresented populations, such as those lacking a spouse, in clinical trials must be increased. Such increases, however, may also necessitate developing methods to reduce informant bias, improve accuracy, and retain participants and study partners. Further studies of predictors of accuracy for informant-based outcomes are also needed.

Collectively, these advances will enhance our ability to detect positive outcomes for effective interventions and to do so in an accelerated timeline.

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