Confirmatory factor analysis (CFA) for cognitive endpoint development: performance characteristics under misspecification, and implications for modeling and analysis

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Methodological Issue Being Addressed There is a great interest in identifying ways to represent cognitive functioning in clinical trial endpoints. Diverse cognitive assessments (e.g., patient-reported outcomes [PROs], clinician-reported outcomes [ClinROs], performance outcomes [PerfOs], sensor-based tools) provide complementary perspectives to inform the overall construct of a patient's level of cognitive functioning, owing to differences arising from self-perception vs external observation. Here we address the methodological need of understanding the importance of the fidelity of composite measures to underlying data generation processes via simulation of hypothetical cognitive assessment data.

Introduction Cognition is a complex construct, and it is unlikely that it can be represented by any single instrument. Combinations of cognitive assessments in endpoints have been studied, although further work is needed to optimize measurement combination. Here, we simulate the modeling of cognitive assessments using Bayesian confirmatory factor analysis (CFA). We hypothesize that CFA will be sensitive to the structure of the input data, as evidenced by CFA model fitting statistics including the root mean-square error of approximation (RMSEA) and cumulative fit indices (CFI).

Methods Simulated data derived from a two-level (higher-order) model. The top-level (random Normal data) represented overall "cognition", and two mid-level factors represented different domains (e.g., memory or executive functioning), with correlations onto the general cognitive factor fixed at 0.7 and 0.8. Each mid-level factor was loaded (magnitudes 0.5-0.8) by six observed variables, yielding 12 simulated items. Final values were derived by adding random Normal error. Simulated data were analyzed using four model architectures. "Model 0" was a single-factor model loaded by all variables. "Model 1" ("naïve" model) was a single-level, two-factor model with either (model 1A) each factor loaded by all variables or (model 1B) each factor loaded by six items. "Model 2" ("true" model) was identical to the data-generating model. "Model 3" was specified with three mid-level factors, to simulate what might happen with three assessment instruments represented (e.g., PRO, ClinRO, and PerfO) instead of two functional domains.
Models were evaluated using metrics such as RMSEA and CFI. Models were fitted using PyMC (v 5.25); sampling was performed using Markov Chain Monte Carlo for 1000 samples with 1000 tuning samples, across 4 chains.

Results Model fit was substantially impacted by model structure. BRMSEA [95% confidence interval] was (from best to worst): Model 2 (0.020 [0.012-0.029])<Model 1A (0.027 [0.018-0.037])<Model 1B (0.047 [0.045-0.051])<Model 3 (0.101 [0.100-0.103])<Model 0 (0.122 [0.121-0.124]). A similar trend was observed using CFI.

Conclusion CFA-based modeling is sensitive to underlying data structure. In our study, the model that respected the true data-generating mechanism performed the best, whereas a naïve model performed the worst. A model that was structured similarly to the true one, but which made different assumptions about the data generation mechanism (i.e., arranging loadings by instrument rather than cognitive construct), performed nearly as poorly as the naïve model. Practically, this means that cognitive endpoints derived from multisource cognitive data require a good understanding of the theoretical relationship(s) between cognitive domains and assessment tools in order to appropriately specify weights of each modality in the composite measure.

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Keywords

Keywords
Latent variable methods
Endpoint development
Cognition

Guidelines I have read and understand the Poster Guidelines

Disclosures The authors are employees of Evinova, which develops digital health tools to support clinical trials.