Title: Towards More Efficient Methods for Clinical Outcome Assessment (COA) Instrument Selection in Alzheimer's Disease (AD) Clinical Trials

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Methodological Question being addressed: A large number of initiatives are being conducted under different approaches to improve efficiency of clinical trials in Alzheimer Disease. A conceptual frame is needed to organize existing initiatives in early/late stages of drug development, to provide a global landscape and to understand the most innovative initiatives.

Objective**:** A first objective is to use our recently created theoretical framework to describe the majority of existing strategies used for COAs selection specific to AD research and second, to explore innovative strategies for endpoint and instrument selection known as efficacy-based selection methods.

Rationale: There is an urgent need in CNS to improve the efficiency of clinical trials. Health outcomes measurement in RCTs is an area of high interaction between several disciplines and different stakeholders. RAs are the main drivers for the final COAs endpoint and instrument selection, which guide the clinical endpoints required to claim a New Drug Application (NDA), followed by field experts on the therapeutic area. COA instrument selection requires a high interdisciplinary methodology. Also specifically in AD, a distinction between early vs late stages of drug development, and between symptomatic vs preventive interventions are needed.

Design**:** We review and describe the **strategies** used so far in clinical trials for COA tools selection in AD, and also those suggested by different partners/stakeholders involved in clinical research as Regulatory Bodies, Scientific Associations/Academia. As for selection strategies we define the use of (a) RA guidance, (b) Results from Published Meta-Analysis, (c) Literature reviews, (d) Libraries of COAs, (e) Libraries of Instruments (f) Authors of the specific instruments (g) Key Opinion Leaders for specific diseases (h) New COAs validation set for specific drug development plans (i) Initiatives to systematize the selection as decision tools i.e. Checklists for COAs selection and for COAs instrument selection. The use of an efficacy-based selection approach within existing COA selection strategies is reviewed.

Results: Different examples for each above specified strategies and stakeholders' categories were identified based on specific searches on public databases and authors' experience in the field. Examples of identified strategies are systematic reviews (e.g., COMET initiative), checklists for instrument selection (COSMIN, EMPRO). Furthermore, other strategies exist coming from alliances (pharma, academia, patients, public health bodies, etc.) promoting COA identification, selection and validation, as is the case of some IMI Initiatives (BD4BO-ROADMAP), NIMH –, Working Groups within Scientific Societies (e.g., ECNP, ISCTM, etc.).

Different examples for each above specified strategies and stakeholders' categories were identified based on specific searches on clinical trials public databases, published peer-review literature and experiences in the field.

***Conclusion*:** The number of trial failures in AD makes COAs and COA instrument selection especially critical. Strategies used so far can be classified using our theoretical framework. In conclusion, overall innovative approaches on endpoint selection will require an approach more focused on *efficacy based COA selection* in order to: (i) Confirm the psychometric features of COAs completed in clinical trials (global and by country-language), (ii) Explore potential derived composite scores as clinical surrogates or endpoints, (iii) Confirm efficiency of COAs used in past trials at global and by country-language level, (iv) explore feasibility of Core Outcome Set (COS) specific for indications, based on qualitative and as well as quantitative methods.