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TOWARDS MORE EFFICIENT METHODS FOR CLINICAL OUTCOME ASSESSMENT (COA) INSTRUMENT SELECTION IN ALZHEIMER'S DISEASE (AD) CLINICAL TRIALS

S. ZARAGOZA DOMINGO[1]; K. BISHOP[2]

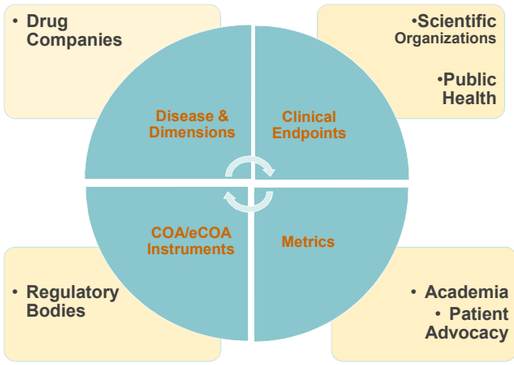
1 Neuropsychological Research Organization s.l., Barcelona, Catalonia, Spain 2 Global Pharma Consultancy, PA, USA

BACKGROUND

A large number of initiatives are being conducted under different approaches to improve efficiency of clinical trials in Alzheimer Disease (AD). A conceptual framework is needed to organize the strategies dealing with Clinical Outcomes Assessment (COAs) issues:

- to identify existing initiatives in early/late stages of drug development
- to provide a global landscape of involved stakeholders
- to identify the most innovative initiatives for COAs instrument selection
- to propose new COAs innovation strategies

Therapeutic Field with High Interaction Among Stakeholders



OBJECTIVES & METHODS

The **first** objective is to identify the stakeholders dealing with COAs in AD clinical trials and to describe existing sources in AD available for COAs selection.

The **second** objective is to describe the most recent innovative strategies for COAs tools selection based on information available.

Information available from published literature and public resources dealing with COAs and COAs tools in AD has been reviewed. The COMPENDIUM FDA initiative and related comments are also included as a source of information in this review.

INNOVATIVE STRATEGIES EFFICACY-BASED COAs SELECTION

Innovative strategies include but are not limited to:

- Identifying biomarkers of disease progression useful to clinical trials for different purposes
- Improve cognitive Composite Scores based on cohort prospective and registry studies
- Exploring potential validity of Composite Scores as clinical surrogates or clinical endpoints
- Confirming psychometrics of COA instruments using data from completed trials (data driven decisions)
- Validating a COS of instruments in AD based on qualitative and quantitative methods
- Confirming validation status for new COAs and eCOAs before their use in drug development i.e. Technology Readiness Level
- Having intense and continuous communication with Regulatory Bodies to define validation road maps (EMA, FDA) for new tools to ensure understanding for endpoints and instrument development.

RELEVANT STAKEHOLDERS IN AD

STAKEHOLDER	ROLE	EXAMPLES
Regulatory Agencies	Research Guidelines	Including Identification of endpoints for each pre-clinical, clinical dementia stage and recommendations for clinical outcomes. • Research Guidelines from **FDA CDER & CBER** • Revised guideline on clinical studies for Alzheimer's disease medicines (EMA)
	COA Qualification	• **FDA/CDER COA DDT** Qualification Program - A regulatory conclusion about a specific COA can be relied upon to have a specific interpretation and application in drug and regulatory review
	COA Validation	• **CPAD** (C-PATH for AD) Partnership with FDA for development of DDTs
	COA Databases	• **COA Compendium** (FDA) (*pilot*) will include COA already been evaluated in the DDT COA Qualification Program or from NME labeling.
Scientific Organizations & National Public Health	Diagnostic Guidance	• **NIA-AA Research Framework supported by NIH** Revised guidelines for Modernization of Diagnostic of AD (ATN System) and 4+ stages system. Diagnostic Recommendations underlying psychopathology.
	Validation new COAs	• **ADCS** Part of the NIA Division of Neuroscience's effort to facilitate the discovery, development and testing of new drugs for the treatment of AD and is part of the Alzheimer's Disease Prevention Initiative - University of California San Diego in 1991 ⇨ ADCS-ADL-MCI, ADCS-ADL, ADCS-MCFSI
Associations & Scientific Organizations	Evaluation	• A-IADL-Q Electronic & Adaptive. **VUmc Alzheimer Center** *(Sikkes et al., 2013)*
	Biomarkers	• **BioFinder**, Skane University Hospital. Identification of early Biomarkers
Drug Companies	Users Drivers of innovation	• Boosting research thorough partnership with academia and health agencies – preventive and symptomatic treatments • Development of Global Scores in Consortia with Research Organizations
Consortia Stakeholders (Academia / Foundations / Researchers / National Public Health)	Accelerate Knowledge Generation & Improve study designs	**Registry** Projects including **Cohort Longitudinal** on several risk factors & biomarkers in AD. Big data useful to generate and validate instruments for specific purposes. Some studies include health participants at risk from general population, health participants relatives of patients or AD patients at different stages. • API Alzheimer Prevention Initiative (Registry) Collaborative Funded by NIH, Philanthropy and Industry • API ADAD - Research on Pre-clinical AD identification Trial Collaborative project involving GNA, the Banner Alzheimer's Institute, Genentech/Roche, and the NIA • ADNI (1, Go, 2&3) and J-ADNI – Focus on Neuroimaging ⇨ **E-COG** Measurement of Everyday Cognition • AIBL, Knight ADRC, MCSA, EMIF-AD,CONCORDE-AD, DIAN, ALFA STUDY • COSMOS-Mind Model for large cognitive trials (outcomes web based and telephonic based) • Harvard Aging Brain Study Alzheimer Center Amsterdam - Identify best cognitive tests • ACT-AD Coalition Group - Speed up Development of potential cures by urging FDA officials, congress and policymakers. • IMAP Sponsored Collaboration with Banner Alzheimer Institute (APCC & RBANS) - Set sensitivity to detect MCI of tests Building cognition global scores as **Composite Scores** ⇨ **ADCOMS** *(Langbaum & Hendrix, 2014)* ⇨ **ADCS-PACC** *(Dononhue et al., 2014)* ⇨ **POWER PACC** (PACC-R) for AD prevention studies *(Hassenstab et al., 2017)* ⇨ **EMACC** *(Jaegger et al., 2017)*

IDENTIFIED COAS INSTRUMENT SELECTION STRATEGIES

SRTATEGY	EXAMPLE	STRENGTHS	WEAKNESS
Critical			
RA Guidelines	• **FDA Early AD: Developing Drugs for Treatment. Guidance for Industry** • **EMA AD Guideline PMP/EWP/553/95 Rev.2**	• Clarification and Directions for future research • Room for negotiation on validating new COAs	• COAs definition not defined enough • Based on *status quo*
Supportive			
Meta-analyses Specific Condition	**Cochrane Library Plus**	• Summary of the State of Art • High quality systematic reviews	• Study selection bias • Not focused on COAs efficiency or sensitivity • Focus on "Intervention" rather than "methods"
Literature Reviews	**Review SCD Measures** *(Rabin, 2015)*	• International scope • Recommendations for instruments selection	• Heterogeneity of studies • Not data-driven.
	COMET Initiative www.comet-initiative.org	• Database of Systematic Review Works • Identification Core Outcomes Set	• Study selection bias • HTA oriented
Enrich Study Sample	**Specific COAs for patient selection** ⇨ RBANS Delayed Memory Index ⇨ A-IADL-Q & Memory **Enrichment Screening - Subjective Decline** ⇨ eCOG *(Farias et al., 2008)* ⇨ SCD-Q *(Rami et al., 2014)*	• Select more homogeneous study samples • Increase probability to have positive biomarker before neuroimaging is performed. • Some COAs validated in large samples (registry/cohorts)	• Several tools available and not always fully validated • Some tools validated in populations different than the ones to be recruited (ex. sociodemographic differences or disease stage).
Instrument Libraries	**ADCS** website **MAPI Trust** **FDA Clinical Outcome Assessments (COA) Qualification & Submissions**	• Useful to collect information of specific instruments • Useful to know copyright holder • Information regarding labelling	• No information about efficacy of measurement instruments • Easily information is out of date
Instruments (authors)	**PerfRO, ClinRO** ADAS Cog, CDR, RBANS	• Complete and first hand information • Support on application and innovation with continuous validation of Composite Scores.	• Copyright limitations • Potential conflict of interests
Clinical Trials Public Databases	Clinicaltrials.gov Clinicaltrialsregister.eu	• List of past and ongoing studies including primary and secondary endpoints	• No information about efficacy of measurement instruments
Checklists / Appraisal forInstrument Selection	**ISPOR** Clinical Outcomes Assessment Emerging Good Practices Task Force **COSMIN, EMPRO**	• Useful to rate the quality of measurement instruments • Useful to guide selection	• List of past and ongoing studies including primary and secondary endpoints • Not specific for Clinical Trials
Database of Projects	**CORDIS** https://cordis.europa.eu/ (EU & EFPIA Funded Projects)	• Identification of validation of new technologies (wearables, etc..) • Existing consortia involving several countries	• Technology validation may need additional funding
Data Processing Standards	• **CDISC**	• Application of CDISC standards to the data generated from a specific measure (i.e. annotated COA).	• A step back from innovative COAs.
Task Force / KOLs for specific condition	• **AADx-CPG** workgroup –Best Clinical Practice Guidelines (CGP) for Clinical evaluation for CBS and ADRD • **CPAD** - Clinically Meaningful Outcomes in Early Alzheimer Disease: A Consortia-Driven Approach to Identifying What Matters to Patients. • **ISCTM** Behavioral and Psychiatric Symptoms in Dementia (BPSD) WG • **ROADMAP** EU-IMI2 "Big Data for Better Outcomes" • **ICHOM Standard Set Dementia**	• Complete and first hand information • Support on application and innovation	• Copyright limitations • Potential conflict of interests • Validation step may not be completed

CONCLUSIONS

New Drug Application (NDA) involves expert advisory groups within the therapeutic area. Specifically, in AD prevention, COA instrument selection requires an interdisciplinary methodology as seen from comments. Approaches that are really innovative use a number of resources. COAs selection should add one step to confirming COAs efficiency using databases from past trials or observational studies.

ACT-AD Accelerate Cure Treatment Alzheimer´s Disease, ADCOMS Alzheimer Disease Composite Score, ADCS Alzheimer Disease Cooperative Study, ADCOMS AD Composite Score, ADCS-ADL Alzheimer Disease Cooperative Study- Activities Daily Living, ADNI Alzheimer Disease Neuroimaging Initiative, ADCS-PACC ADCS Preclinical Alzheimer Cognitive Composite, ADRD Alzheimer Disease and Related Dementias, A-IADL-Q Instrumental Activities of Daily Living Questionnaire, AIBL The Australian Imaging, Biomarker & Lifestyle Flagship Study of ADCS AD Cooperative Study, API Alzheimer Prevention Initiative, BIOFINDER Biomarkers for Identifying, Neurodegenerative Disorders Early and Reliably, CBER Center for Biologics Evaluation and Research, CBS Cognitive Behavioral Syndromes, CDISC Center for Data Interchange Standards Consortia, COMET Core Outcome Measures in Effectiveness Trials, CONCORD-AD Connecting Cohorts to Diminish AD, COS Core Outcomes Set, COSMIN Consensus-based Standards for the Selection of Health Measurement Instruments CDR Clinical Dementia Rating scale, EMPRO Evaluating Measures of Patient Reported Outcomes, COSMOS Mind Cocoa Supplement and Multivitamin Outcomes Study in the Mind, CPAD Critical Path For Alzheimer's Disease, C-PATH Critical Path Institute, DDT Drug Development Tools, DIAN Dominantly Inherited Alzheimer's Network, EMACC Early AD/ MCI Alzheimer's Cognitive Composite, EMIF-AD European Information Framework - Alzheimer's Disease, EPAD European Prevention Dementia Registry, EPAD-LCS European Prevention Dementia Registry Longitudinal Cohort Study, FDA CDER Center for Drug Evaluation and Research, GNA Neurosciences Research of Antioquia, HTA Health Technology Agency, IMAP Insights to Model Alzheimer Progression in Real Life, ICHOM International Consortium for Health Outcomes Measurement KOL Key Opinion Leader, MCSA Mayo Clinic Study of Aging, MIF-AD European Medical Information Framework for Alzheimer's, NIA National Institute of Aging, NIA-AA National Institute on Aging and Alzheimer's Association, NME New Molecular Entity PACC Preclinical Alzheimer Cognitive Composite, PROMIS Patient-Reported Outcomes Measurement Information System, ROADMAP Real world outcomes across the AD spectrum for better care: multi-modal data access platform.

@neuropsynchro

Global Pharma Consultancy