Choosing Clinical Outcomes Assessments for Angelman Syndrome: Challenges and Potential Solutions in Rare Diseases

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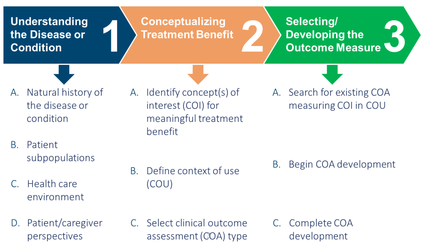
Introduction

Angelman Syndrome (AS) is a rare (1/15,000) neurogenetic disorder characterized by developmental delay, movement disorder, behaviour disturbance, speech impairment, seizures and sleeping problems.

There are no therapies for AS and no established patient-focused Clinical Outcomes Assessments (COA) for use in trials specific to AS.

This study was designed to create a conceptual model and select outcome measures for a Phase II AS clinical study, following FDA guidance (Figure 1).

Figure 1: Roadmap to Patient-Focused Outcome Measurement in Clinical Trials



Methods

To identify key concepts that guided the literature search, informal discussions were held with clinical experts, advocacy groups, and parents of children with AS.

A targeted literature search was conducted using PubMed to identify key concepts and COAs that may be relevant; clinicaltrials.org to identify ongoing studies and any COA's currently used; the FDA website to identify COAs that are approved, recommended or under review for FDA certification in the concepts of interest; and Google to identify unpublished COA.

Pubmed searches were conducted for English language articles as follows:

- ❑ Angelman Syndrome or Fragile X and
  - Qualitative or focus group or interview or impact (no time limit)
- ❑ Angelman Syndrome or Fragile X and
  - Behaviour or Motor or mobility or Sleep or Communication or language (no time limit)
- ❑ Rett Syndrome (limit of 5 years) and
  - Behaviour or Motor or mobility or Sleep or Communication or language and
  - Measure or assessment or questionnaire
- ❑ Pompe Disease or Cerebral Palsy (limit of 5 years) and
  - Motor or mobility or functioning and gait and
  - Measure or assessment or questionnaire
- ❑ Caregiver and
  - Impact or burden or functioning or well-being or mental health (no time limit)

Clinicaltrials.org search for outcomes used in studies of:

- ❑ Angelman Syndrome, Fragile X, Rett Syndrome, Pompe Disease, and Cerebral Palsy

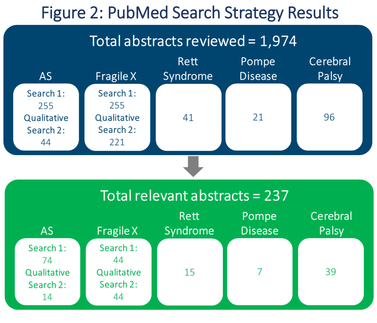
Articles were included if they had key words in the abstract. For the conceptual model, articles were included if the abstracts stated concepts that were impacted by AS either qualitatively or quantitatively. For instrument identification, articles must have referred to a COA in the abstract (preferably by name).

An instrument was short-listed for further assessment of psychometric properties if it:

- ❑ Covered any one (or more) of the key concepts of interest AND
- ❑ Was used in AS or Fragile X OR
- ❑ Was used in other similar or relevant rare diseases in a reputable study OR
- ❑ Has been accepted (or in process) by FDA OR
- ❑ Was responsive to treatment in a clinical trial in a related disease area

Figure 2 provides an overview of the search strategy results.

Figure 2: PubMed Search Strategy Results

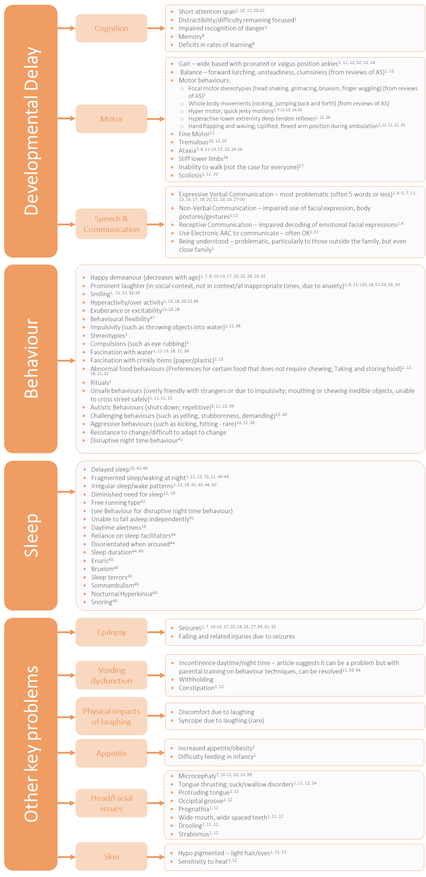


Results

Relevant Concepts in Angelman Syndrome

- ❑ The conceptual model highlights developmental delay (motor, cognition, and speech), behavior and sleep as the key concepts identified as important in the literature and during our discussions with caregivers, advocacy groups and clinicians (Figure 3).
- ❑ The impact of AS on the patients' activities of daily living, independence, emotions and social life were profound. [1]
- ❑ Possible mediators of these concepts included AS genotype, [1-13] age, [5, 14-18] seizure activity, [5] and current child state (such as stress, excitement, or boredom). [1]
- ❑ Caregiver's mental and physical health, as well as their sleep, work and social lives were impacted by AS. [19]

Figure 3: Draft Conceptual Model for Angelman Syndrome based on Literature Review



Identified instruments

Figures 4 provides an overview of the identified questionnaires. No instruments were specifically developed for AS, though several measures were used in AS studies and in related neurodevelopmental diseases. All cognition scales and the majority of motor scales (10) were performance outcomes or clinician administered. The majority of behavior (12) , sleep (4), and communication (2) measures were observer reported outcomes. Five motor, three cognition, five behavior, and one sleep measure were mentioned on the FDA website in labels, guidance, the qualification compendium, or safety tracking. No communications or caregiver impact measures were found on the FDA website. Likely treatment benefits and study design would influence COA choice and the need for adaptation to ensure a 'fit for purpose' patient-centered strategy.

Figure 4: Overview of instruments identified in the literature

Behaviour Instruments

Vineland Adaptive Behaviour[4, 8, 13, 55-57]
Aberrant Behaviour Checklist[4, 18, 57-63]
Children's Social Behaviour Questionnaire[71, 72]
Child Behaviour Checklist[57]
Behaviour Flexibility rating scale, revised[37]
Gilliam Autism Rating scale[57]
Developmental behaviour checklist[21, 69, 70]
Reiss Screening tool for maladaptive behaviour[38, 61, 64-68]
Socially Appropriate behaviour questionnaire
Night-time behaviour
Overt Agitation Severity Scale[73]
Modified Overt Aggression Scale[74, 75]
Behaviour Problems Inventory[62, 76, 77]
Child's Challenging Behaviour Scale[78, 79]
Challenging Behaviour Questionnaire[81]
Challenging Behaviour Checklist[81]
Anxiety, Depression and Mood Scale[63, 82, 83]
Overt Aggression Scale[84]

Sleep Instruments

Behavioural Evaluation of disorders of sleep[85, 86]
Diary for sleep[41,43]
Polysomnography[15, 19, 49, 87]
Actigraphy/Actiwatch[41, 88-90]
Children's Sleep Habits Questionnaire[19, 91]
Pediatric Sleep Questionnaire[92, 93]

Motor Instruments

Trunk stability
Zeno Walkway System[94-98]
6 minute walk test[99-105]
Modified Ashworth Scale[94, 106, 107]
Modified Tardieu Scale[94]
Gross Motor Function Measure[94, 106-115]
Paediatric Evaluation of Disability Inventory[96, 110, 115-119]
Modified Performance Oriented Mobility Assessment-Gait (MPOMA-G) scale[120]
Activities Scale for Kids[121]
Berg Balance Scale[103]
ACTIVE-Kinect
Child Health Assessment Questionnaire[122]

Communication Instruments

AAC – type of communication questionnaire[2, 31, 123, 124]
Choice Assessment Scale[38]
Perceptions of communication patterns
Satisfaction with AAC
Social Communication Questionnaire[125]
Receptive-Expressive-Emergent Language Scale (REEL-2)[30]
Stark Assessment of Early Vocal Development-Revised[126]

Cognitive Instruments

Bayley Scales of Infant and Toddler Development[4,8,13]
Wechsler[55]
Griffiths Mental Development Scale[30]
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[127]
Kaufman Assessment Battery for Children-Luria (non-verbal)[128, 129]

Caregiver Instruments

Choice Assessment Scale[38]
Parenting Stress Index –Short[57, 130-133]
SF-36[134]
Measures of Processes of Care
Coping Health Inventory for Parents
Family Impact Scale[135-138]
Impact-on-Family Scale[139-142]

Discussion and Conclusions

Our study highlights patient-relevant and potentially appropriate measures that could be used in AS clinical trials. The identified measures meet some, if not all, of FDA guidance for COA assessments in related diseases, but in AS specifically content validity and responsiveness are not always available. Where there are no pre-existing specific measures in a rare disease with high unmet need, COA research is needed to ensure 'fit for purpose' outcomes are used in trials to demonstrate drug efficacy.

In order to ensure that treatments are not delayed due to lack of validated measurement strategies in rare disease populations, methods need to be used that are appropriately robust but pragmatic, taking into account the small patient populations. In addition to standard searches in PubMed, Google searches and discussions with advocacy groups and health care professionals helped us to find instruments to evaluate, as well as to discover new, promising, but unpublished measures. These newer measures can be correlated with older, well-validated measures in early phase clinical trials to ensure that relevant and responsive instruments are chosen for later phase trials. Capturing caregivers' (or patients' in rare diseases where that is possible) perspectives and feedback throughout the process can ensure that the selected COA strategy is relevant and feasible. In addition, collaboration with regulators is essential to ensure appropriate endpoint choices as we go down uncharted territory. When successfully implemented, all stakeholders benefit, most importantly, the patients themselves.

References Provided upon request; please contact Linda.Abetz-Webb@p-coa.com for more information