

# **How to identify relevant disease domains in a heterogeneous, multi-domain syndrome?**

*Measuring what matters: a case study from Angelman syndrome*

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EFSPI, 20<sup>th</sup> August 2026

## **Disclaimers:**

The views and opinions described are my own and not necessarily those of Roche

The Ph3 design presented was terminated prior to its initiation. Development was subsequently transitioned to another company.

# Key Takeaways

- 01 Multi-System Disease Strategy**  
 Multi-system diseases (like AS) require multi-domain endpoints to capture total treatment effect.
- 02 Qualitative Research Drives Strategy & Content Validity**  
 Required by regulators to demonstrate how meaningful aspects of health are identified, selected and prioritized, guiding domain selection and justifying COAs.
- 03 FDA Multiple Endpoint Guidance**  
 Supports multi-domain endpoints with appropriate adjustment for multiplicity.
- 04 Dual-Purpose Global Impressions**  
 Can holistically assess heterogeneous conditions, and used as an anchor to calculate meaningful change thresholds.

# Angelman syndrome (AS) is a rare neurodevelopmental disorder caused by the lack of expression of UBE3A in neurons

- **AS is a monogenetic rare neurodevelopmental disease causing symptoms over a broad range of domains**
- **Currently no available treatments**

Occurs in ~1 in 12–20,000 births<sup>1</sup>



AS is characterized by life-limiting features<sup>2</sup>

Lack of ability to speak

Seizures

Severe cognitive impairment

Aggression, Hyperactivity

Motor impairments

Self injury

Sleep disturbances

Never live independently

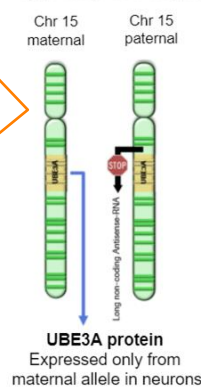


T. Willgoss et al, 2021, Measuring What Matters to Individuals with Angelman Syndrome and Their Families: Development of a Patient-Centered Disease Concept Model, Child Psych Hum Dev 52 (4): 654-668

**The disease-modifying potential of this antisense oligonucleotide**   
**Unsilencing the paternally imprinted allele.**

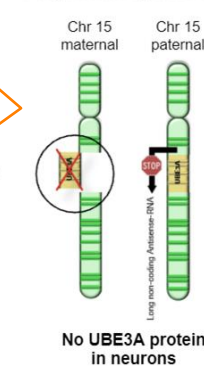
in typically developing people neurons express UBE3A only from the maternal allele, the paternal allele is silenced

Typically developing



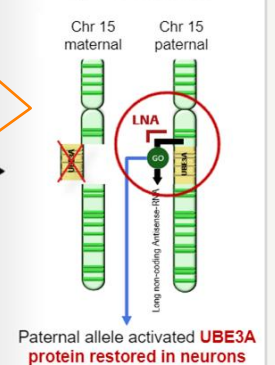
in Angelman Syndrome (AS) the maternal allele is either lost or defect through mutations or deletion

Angelman syndrome



Rugonersen binds to the antisense-RNA which silences the paternal allele to restore mono-allelic expression of UBE3A in neurons

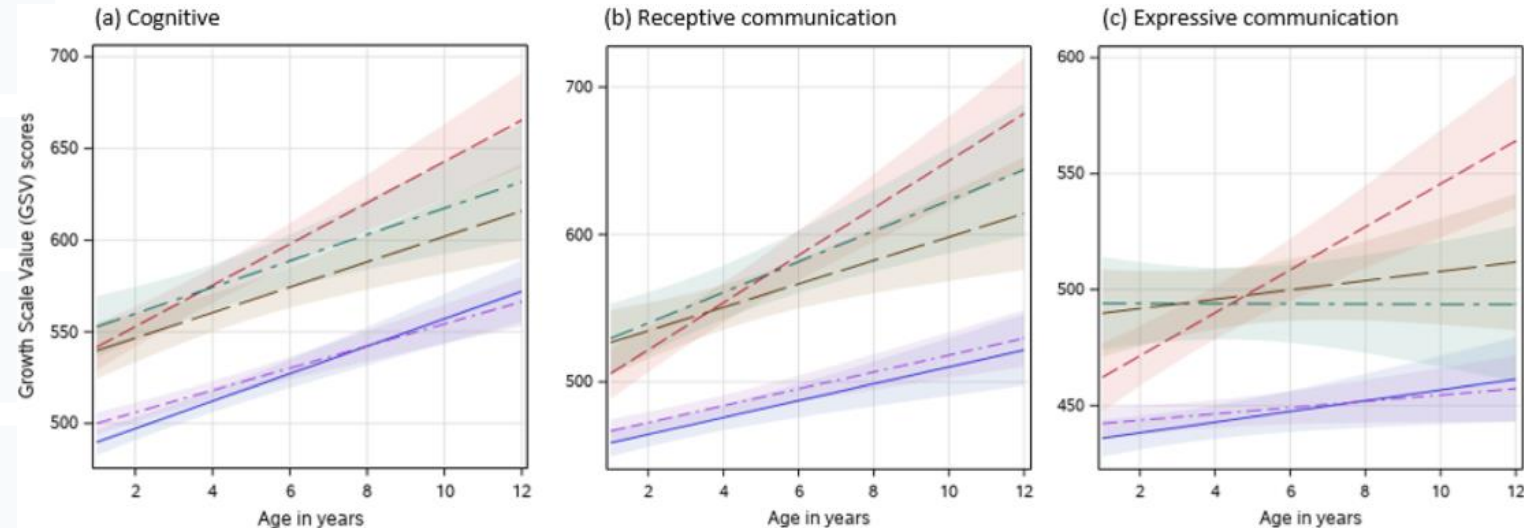
Upon treatment



# Challenges & Considerations Designing Pivotal Ph3

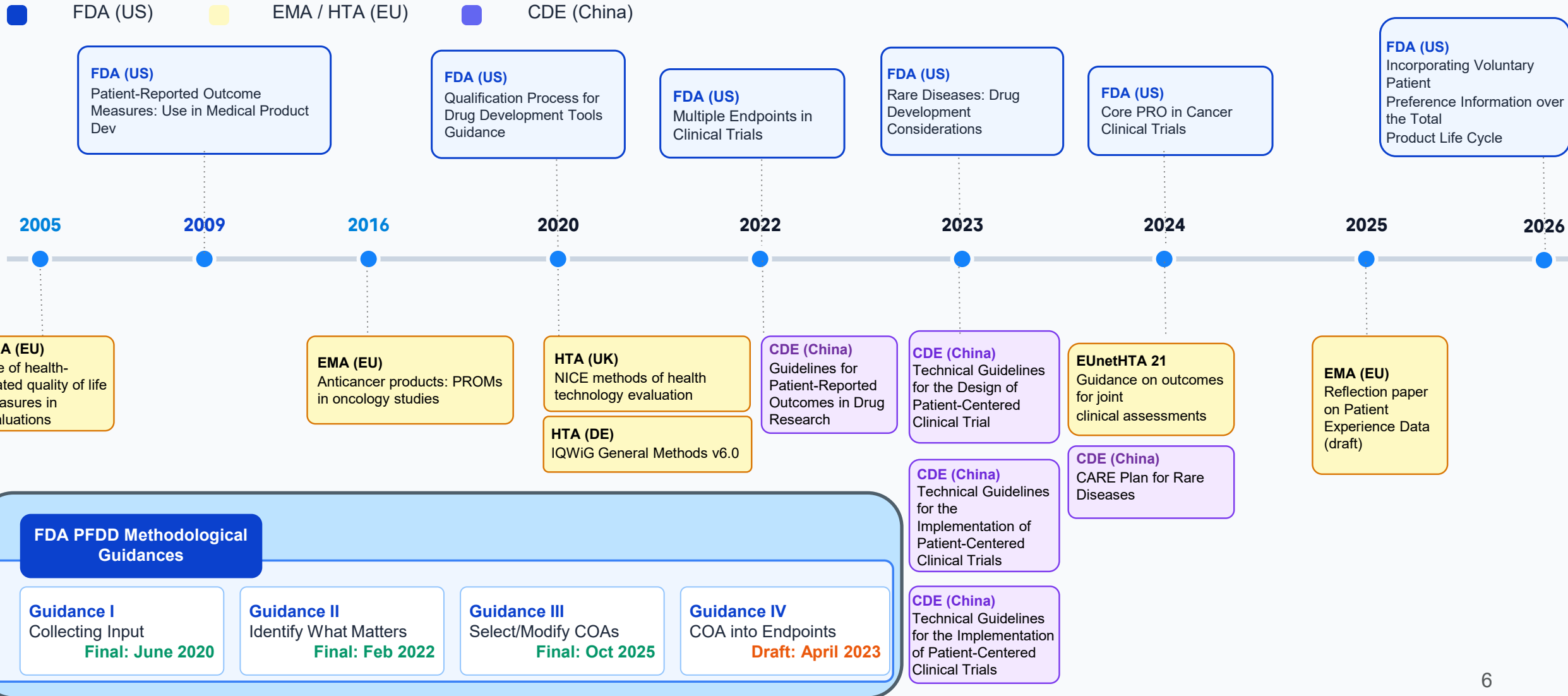
Team challenge: What primary and key secondary endpoints do we use for our planned AS Ph3?

- **Rare**
- **Heterogeneous**
- **Limited natural history data**
- **No obvious 1EP** - limitations to available clinical outcome assessments
- **Development differs** from 0-4 and 5-12 year olds Do we need a different 1EP for each age group?



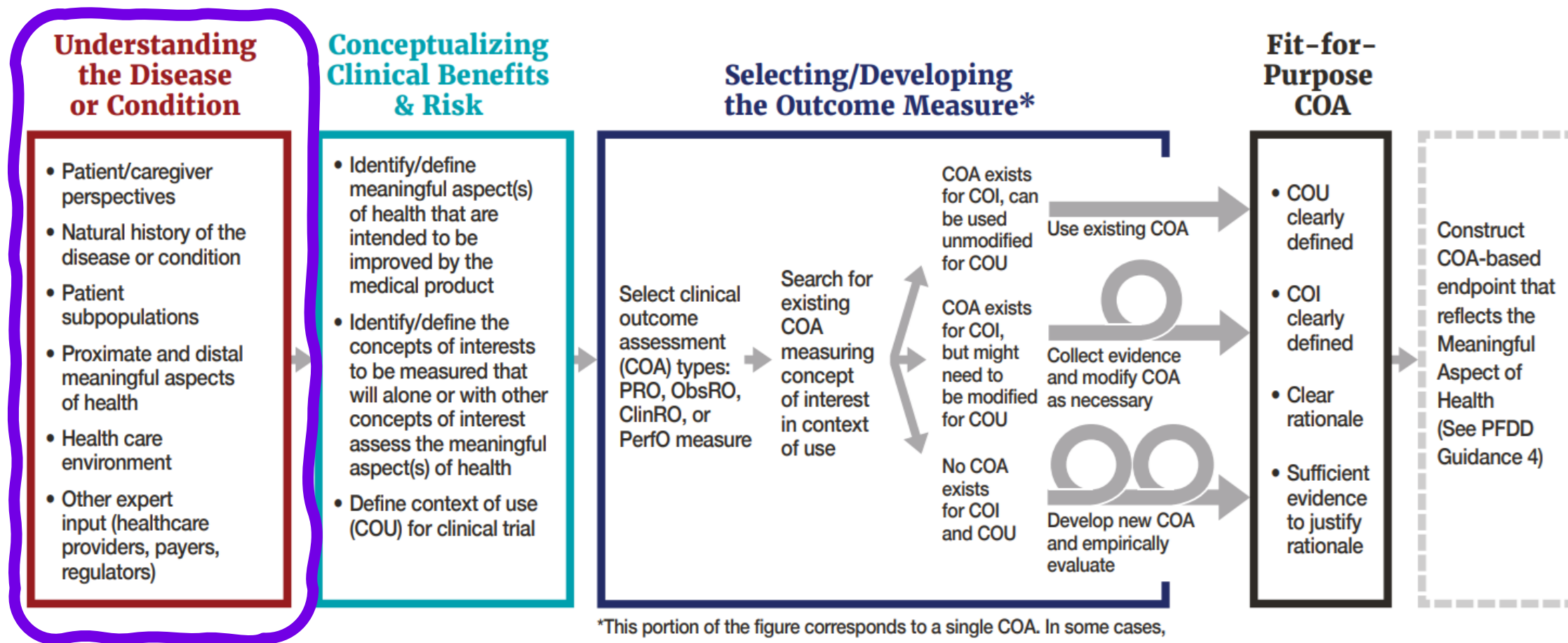
# Measuring what matters - A regulatory/HTA perspective

*Takeaway: Guidance on COA development is generally consistent across HAs*



# How to identify relevant disease domains in a heterogeneous, multi-domain syndrome?

Takeaway: Qualitative data forms the conceptual foundation that justifies domain selection





# Measuring what matters

*A disease concept model informed by clinicians, patient advocacy groups and patients / families*



- Semi-structured telephone interviews were conducted with AS caregivers (n=30) and clinical experts (n=3)
- Interview transcripts were reviewed, coded, themed and quantified
- Core disease concepts reached data saturation within the first 10 caregiver interviews, and secondary concepts saturated within 20 interviews

| AS Defining Concepts                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Neurological                                                                                                                                                                                                                                                                                                       | Musculoskeletal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Gastrointestinal                                                                                                                                                                                                                                                                                           | Skin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Visual                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                              |
| <ul style="list-style-type: none"> <li>• Seizures</li> <li>• Microcephaly*</li> <li>• Dysmyelination on MRI**</li> <li>• Abnormal EEG***</li> <li>• Low muscle tone (hypotonia)</li> <li>• Ataxia</li> <li>• Tremors</li> <li>• Lack of neuroplasticity****</li> <li>• Abnormal circadian*****responses</li> </ul> | <ul style="list-style-type: none"> <li>• Increased curve in spine (Scoliosis or excessive lumbar curve)</li> <li>• Ankle pronation (inward rolling of ankle and foot)</li> <li>• Craniofacial abnormalities (prominent mandible, wide mouth, flat back of head)</li> <li>• Osteoporosis</li> </ul>                                                                                                                                                                                                                               | <ul style="list-style-type: none"> <li>• Reflux</li> <li>• Vomiting</li> <li>• Obesity</li> <li>• Esophagitis</li> <li>• Constipation</li> <li>• Incontinence</li> </ul>                                                                                                                                   | <ul style="list-style-type: none"> <li>• Eczema</li> <li>• Hypo-pigmented</li> <li>• Increased sensitivity to heat and sun</li> <li>• Poor temperature regulation</li> <li>• Absence of sweating</li> </ul>                                                                                                                                                                                                                                                                              | <ul style="list-style-type: none"> <li>• Increased sensitivity to light</li> <li>• Strabismus (abnormal eye movements, tracking difficulties)</li> <li>• Visual impairment</li> </ul> |                                                                                                                                                                                                                                                                                                                                              |
| Cognition                                                                                                                                                                                                                                                                                                          | Motor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Communication                                                                                                                                                                                                                                                                                              | Behavior                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Emotion                                                                                                                                                                               | Sleep                                                                                                                                                                                                                                                                                                                                        |
| <ul style="list-style-type: none"> <li>• Learning deficit</li> <li>• Memory challenges</li> <li>• Attention deficit</li> </ul>                                                                                                                                                                                     | <ul style="list-style-type: none"> <li>• Delayed motor skills</li> <li>• Oral motor impairment: tongue thrusting, sucking and swallowing disorders, frequent drooling, excessive chewing, mouthing behaviors, and feeding difficulties</li> <li>• Regression in FM/GM***** skills with age</li> <li>• Dyspraxia - impaired ability to complete coordinated movements</li> <li>• Gait - wide based, ataxic with uplifted arms and pronated ankles</li> <li>• Balance - unsteady</li> <li>• Tremulous movement of limbs</li> </ul> | <ul style="list-style-type: none"> <li>• Decreased receptive communication</li> <li>• Decreased expressive communication*****</li> <li>• Non-verbal communication through use of facial expression, body postures and gestures</li> <li>• May use alternative and/or augmentative communication</li> </ul> | <ul style="list-style-type: none"> <li>• Frequent laughter/smiling, happy demeanor</li> <li>• Easily excitable-hyperactivity, increased impulsivity</li> <li>• Maladaptive behaviors: biting, hair-pulling, pinching, slapping</li> <li>• Increased lethargy with age</li> <li>• Hand flapping or waving movements</li> <li>• Increased exploratory mobility</li> <li>• Fascination with water and crinkly items</li> <li>• Food seeking behaviors</li> <li>• Temper tantrums</li> </ul> | <ul style="list-style-type: none"> <li>• Increased fear</li> <li>• Anxiety/panic attacks</li> <li>• Frustration</li> </ul>                                                            | <ul style="list-style-type: none"> <li>• Abnormal Sleep wake cycle</li> <li>• Issues with initiation and maintenance of sleep</li> <li>• Sleep terrors</li> <li>• Nighttime epilepsy</li> <li>• Disorientation when aroused</li> <li>• Snoring and teeth grinding</li> <li>• Bed wetting (day and night)</li> <li>• Sleep walking</li> </ul> |

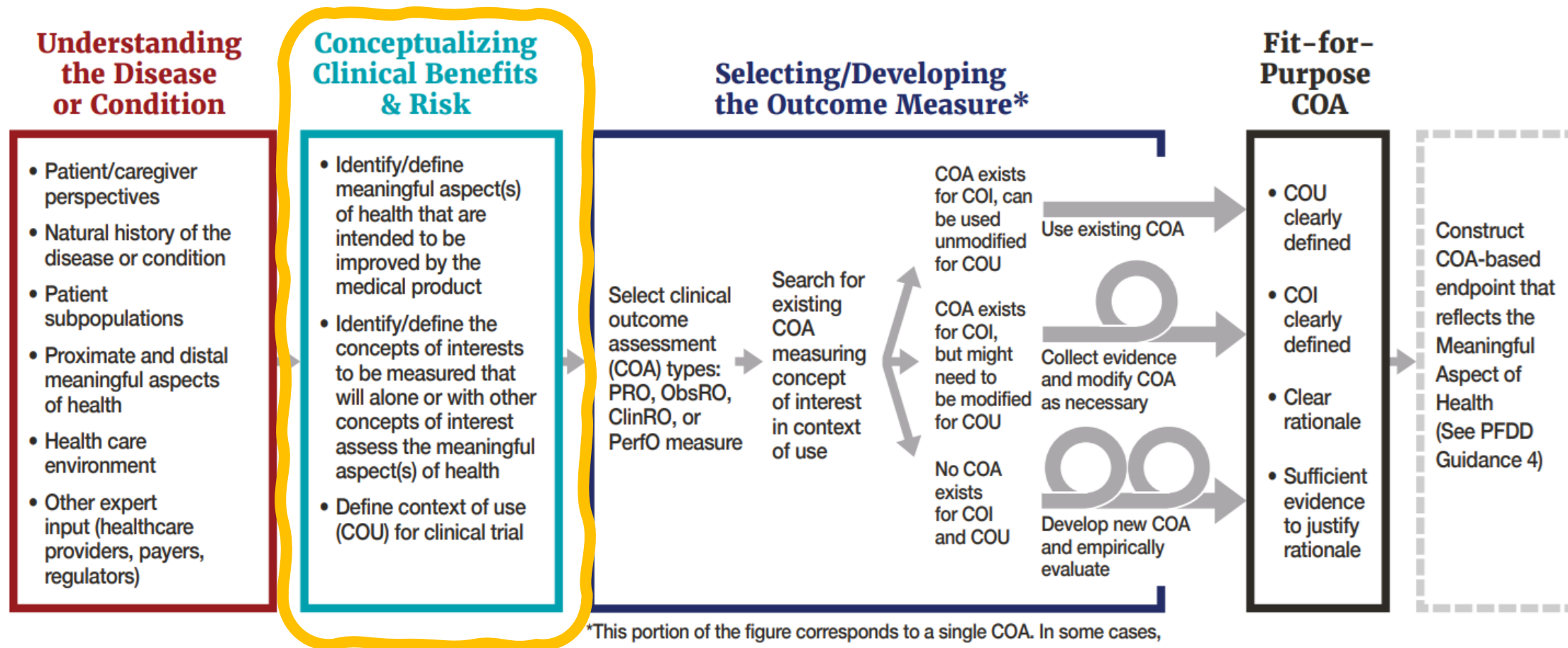
| Cognition                                                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Learning deficit</li> <li>• Memory challenges</li> <li>• Attention deficit</li> </ul> |

| AS individual Impact Concepts                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                  |                               |                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Proximal Impact Concepts                                                                                                                                                                                                                                                                                                                                                                      | Distal Impact Concepts                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                  |                               |                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                 |
| Self care and activities of daily living                                                                                                                                                                                                                                                                                                                                                      | Participation/Engagement in Age Appropriate Life Situations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                  |                               |                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>• General lack of independence</li> <li>• Difficulty in dressing</li> <li>• Difficulty in bathing</li> <li>• Difficulty in feeding/ eating</li> <li>• Inability to use toilet</li> <li>• Difficulty in doing household tasks</li> </ul>                                                                                                                | <table> <tr> <th>Community/School</th><th>Socialization and Family Life</th></tr> <tr> <td> <ul style="list-style-type: none"> <li>• Decreased recognition of danger</li> <li>• May be overly friendly and impulsive with strangers</li> <li>• Unable to safely cross street</li> <li>• Difficulty adapting to change</li> <li>• Being understood outside the family may be problematic</li> <li>• Academic challenges-supportive educational needs</li> <li>• Special schools</li> </ul> </td><td> <ul style="list-style-type: none"> <li>• Capable of social engagement and establishing intentional relationships, may be overly affectionate</li> <li>• Laughter not always in social context?</li> <li>• Challenging social behaviors such as yelling, stubbornness demanding, or withdrawn</li> <li>• Inappropriate or socially impulsive behavior, may greet people with grabbing</li> </ul> </td></tr> </table> | Community/School | Socialization and Family Life | <ul style="list-style-type: none"> <li>• Decreased recognition of danger</li> <li>• May be overly friendly and impulsive with strangers</li> <li>• Unable to safely cross street</li> <li>• Difficulty adapting to change</li> <li>• Being understood outside the family may be problematic</li> <li>• Academic challenges-supportive educational needs</li> <li>• Special schools</li> </ul> | <ul style="list-style-type: none"> <li>• Capable of social engagement and establishing intentional relationships, may be overly affectionate</li> <li>• Laughter not always in social context?</li> <li>• Challenging social behaviors such as yelling, stubbornness demanding, or withdrawn</li> <li>• Inappropriate or socially impulsive behavior, may greet people with grabbing</li> </ul> |
| Community/School                                                                                                                                                                                                                                                                                                                                                                              | Socialization and Family Life                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                  |                               |                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                 |
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# How to identify relevant disease domains in a heterogeneous, multi-domain syndrome?

*Takeaway: Qualitative data forms the conceptual foundation that justifies domain selection*



\*This portion of the figure corresponds to a single COA. In some cases, multiple COAs might need to be used to capture a single MAH. In those cases, the path reflected here would be followed for each COA.

# Measuring what matters



*Clinician plus patient and/or caregiver input on prevalence, frequency and impact of concepts*

## Selecting key concepts of interest

- What is most important to patients?
- What are the clinically disease-defining concepts vs impacts?
- What is the prevalence, frequency and impact?

| Concept                | Lifetime prevalence | AS conceptual model | Key considerations                          |
|------------------------|---------------------|---------------------|---------------------------------------------|
| Communication          | 100%                | Disease defining    | High clinical importance experienced by all |
| Motor skills           | 100%                | Disease defining    |                                             |
| Cognition              | 100%                | Disease defining    |                                             |
| Self-care              | 100%                | Impact of AS        | Consequence of                              |
| Seizures               | >80%                | Disease defining    | Not universal, medicated                    |
| Sleep problems         | 20-80%              | Disease defining    | Not universal                               |
| Maladaptive behaviours | 20-80%              | Disease defining    | Not universal                               |
| Social difficulties    | N/A*                | Impact of AS        | Distal impact                               |

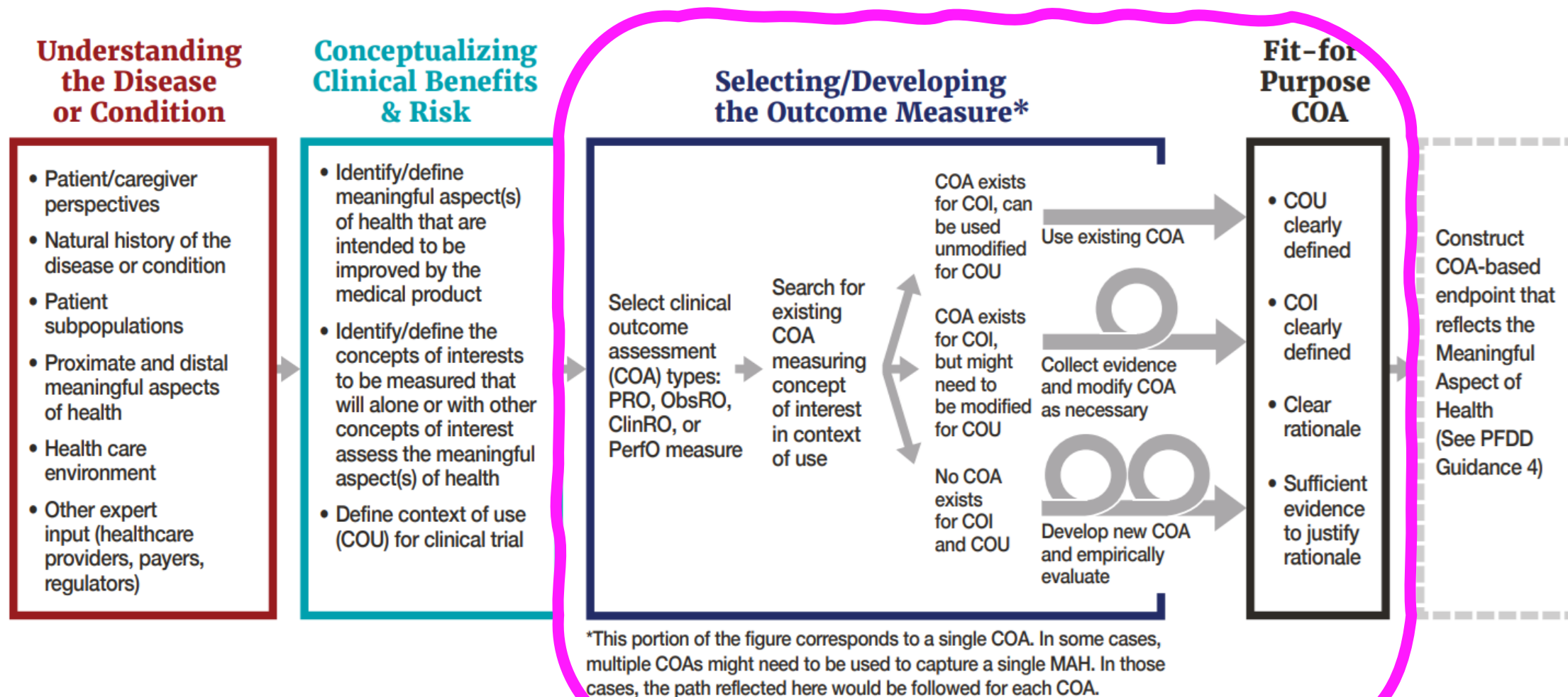
## Why This Matters

Capturing this data provides empirical justification for **why** specific endpoints are chosen, **how** they should be measured, and **when** it should be captured.

\*Social difficulties are a distal impact, which is multifactorial (e.g environmental, symptoms, support systems etc), meaning lifetime prevalence will be variable from person to person

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# COA Deep Dives

*Recurring structure allowed consistent assessment of measures*

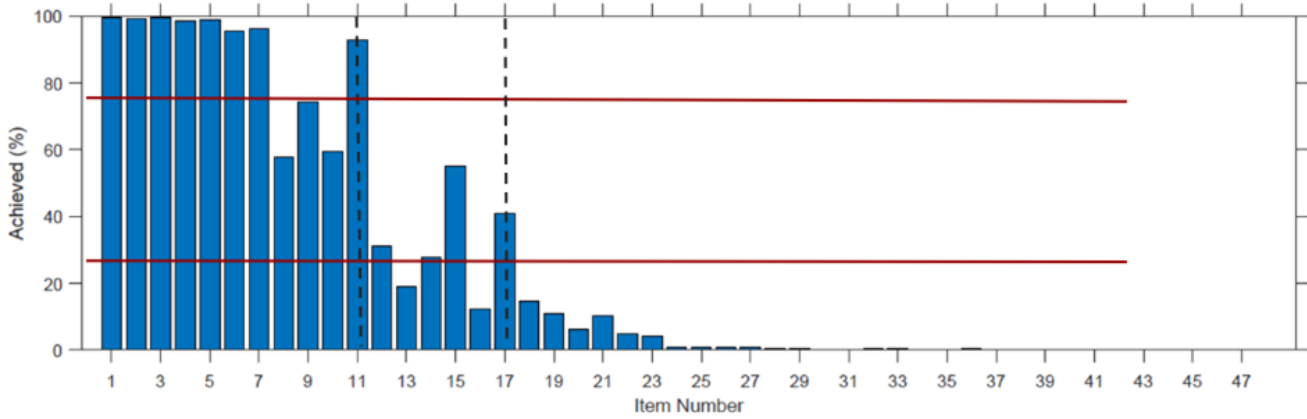
## Assess the appropriateness of each measure

- 1. Conceptual relevance:** Compare conceptual target domains to COA
- 2. Instrument summary:** Structure, administration
- 3. Item analysis:** Overview & comparison to relevant measures
- 4. Scoring:** Available metrics - pros & cons
- 5. Data insights:** Prior literature & natural history data (e.g. FREESIAS)
- 6. Regulatory guidance & feedback**
- 7. SWOT analysis**

## (2) Instrument Summary: Mapping of concepts to each measure & comparison

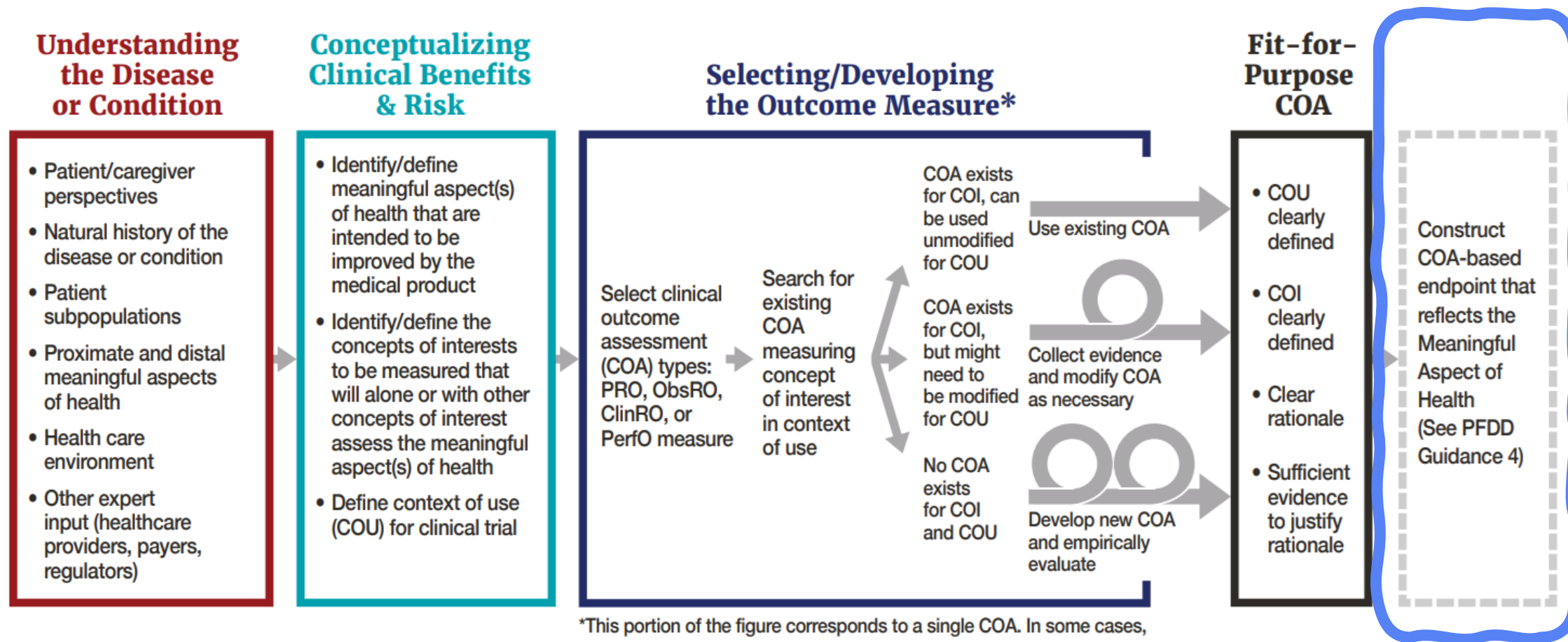
| Target domain/<br>concept | Lifetime<br>prevalence | Position within<br>AS Conceptual<br>model | Key considerations                                                                          | Clinical Outcome Measures |        |                         |      |         |
|---------------------------|------------------------|-------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------|--------|-------------------------|------|---------|
|                           |                        |                                           |                                                                                             | Bayley                    | VABS-3 | Communication<br>Matrix | ORCA | SAS-CGI |
| Communication             | 100%                   | Disease defining                          | High clinical importance<br>Experienced by all                                              | X                         | X      | X                       | X    | X       |
| Motor Skills              | 100%                   | Disease defining                          |                                                                                             | X                         | X      |                         |      | X       |
| Cognition                 | 100%                   | Disease defining                          |                                                                                             | X                         |        |                         |      | X       |
| Self-care                 | 100%                   | Impact of AS                              | Functional impacts are<br>secondary to communication,<br>motor and cognition<br>impairments |                           | X      |                         |      | X       |
| Seizures                  | >80%                   | Disease defining                          | Not experienced by all and<br>typically managed by<br>medication                            |                           |        |                         |      | X       |
| Sleep problems            | 20%-80%                | Disease defining                          | Not experienced by all                                                                      |                           |        |                         |      | X       |
| Maladaptive<br>behaviors  | 20%-80%                | Disease defining                          | Not experienced by all                                                                      |                           | [X]    |                         |      | X       |
| Social                    | N/A                    | Impact of AS                              | Distal impact; can be strength /<br>resource                                                |                           | X      |                         |      |         |

## (3) Item Analysis: Detailed item analysis & comparison to other measures



# How to identify relevant disease domains in a heterogeneous, multi-domain syndrome?

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\*This portion of the figure corresponds to a single COA. In some cases, multiple COAs might need to be used to capture a single MAH. In those cases, the path reflected here would be followed for each COA.



# Primary endpoint construction options

Theme “**Failure to account for multiplicity** when there are several endpoints evaluated in a study **can increase the chance of false conclusions** regarding the effects of the drug.....concern regarding multiplicity arises principally in the evaluation of clinical trials intended to demonstrate effectiveness supporting drug approval and claims in FDA-approved labeling”

## Primary Endpoint Family

*An effect on any one of disease aspects could support a conclusion of effectiveness*

**Strength:** Flexibility (any one can show improvement)

**Consideration:** Adjustment for Type 1 error is required to address multiplicity

**Example:** Burn wounds (rate of wound closure vs. reduced scarring)

## Co-primary

*Required demonstration of treatment effect on all specified features to establish efficacy*

**Strength:** Useful when multiple outcomes are necessary for clinical benefit

**Consideration:** High Type II error risk (cannot easily increase alpha to offset power loss)

**Example:** Migraine (demonstrating effect on both pain and photophobia)

## Composites

*Combination of more than one clinical outcome into a single variable*

**Strength:** Improves statistical efficiency, precision, and power to measure small effects

**Consideration:** Requires similar importance; lesser events must not drive the overall outcome

**Example:** Major adverse clinical outcome events (MACE) in cardiovascular disease, ie. composite of myocardial infarction, stroke, death

## Multi-component Endpoints

*Within-subject combination of two or more components into an overall score*

**Strength:** Allows single evaluation of numerous components without multiplicity issues

**Consideration:** Individual components need to be weighted appropriately

**Example:** Positive and Negative Syndrome Scale (PANSS) in schizophrenia

## Multiple Endpoints in Clinical Trials Guidance for Industry

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

October 2022  
Biostatistics

## FDA Guidance for Industry

*"This guidance provides sponsors and review staff with the Agency's thinking about the **problems posed by multiple endpoints** in the analysis and interpretation of study results and **how these problems can be managed in clinical trials.**"*

FDA's 2022 Multiple Endpoints Guidance

**PCOR** *measuring what matters to patients.*

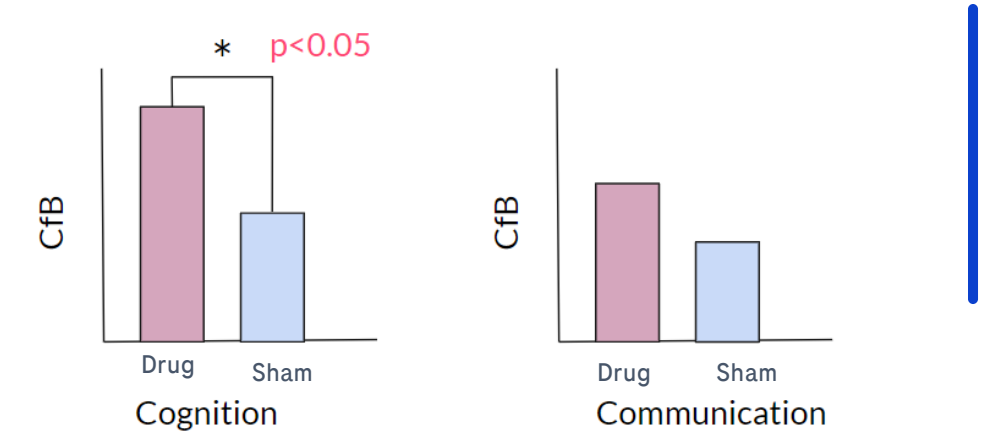


# Proposed primary endpoint construction

Primary endpoint family: Change on at least 1 of 2 concepts

| Concept                                  | Reason selected                                            | 0-4 years                                                                                                 | 5-12 years |
|------------------------------------------|------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|------------|
| Communication (expressive and receptive) | Voiced as the most meaningful                              | Average of the Growth Scale Value (GSV) score of the Bayley-4 expressive and receptive subtest (combined) |            |
| Cognition                                | Foundational symptom, ranked as one of the most meaningful | GSV score of the Bayley-4 cognitive subtest                                                               |            |

Example:



- Each domain analysed, separately, on a continuous scale at day [EoT]
- Statistical Test: comparison between Treatment groups of **mean change from baseline** for the two concepts
- Success: if either one of the two concepts (or both) show statistically significant difference from baseline between active arm and Sham.

# Importance of clinical meaningfulness in COA Endpoints



*Supporting statistical significance with clinically meaningful patient outcomes*

## **FDA PFDD 4:**

*“Statistical significance does not, by itself, indicate whether the detected effect corresponds to a clinically meaningful treatment effect.”*

## **Within-Patient Meaningful Change Threshold (wpMCT)**

### **Regulator Focus — Evaluation of Treatment Meaningfulness**

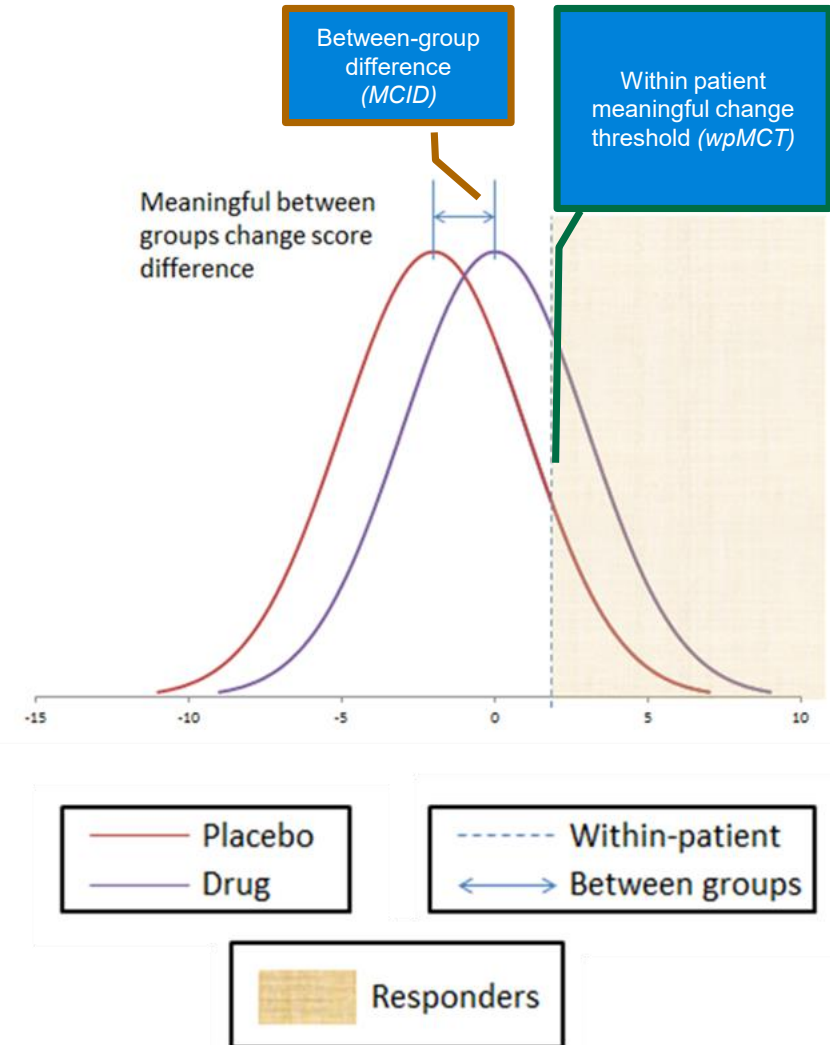
Determines the proportion of patients with a meaningful level of improvement or worsening depending on the condition. Essential for regulatory evaluations.

## **Between-Group Difference (MCID)**

### **Internal Planning Focus — Trial Design & Strategy**

Evaluates the overall size of the delta between arms at the end of a trial. Primarily useful for internal strategic planning.

**Note: Although these values are related, they represent distinct concepts.**



# Group difference vs individual difference on scale-based endpoints

## within-patient MCT

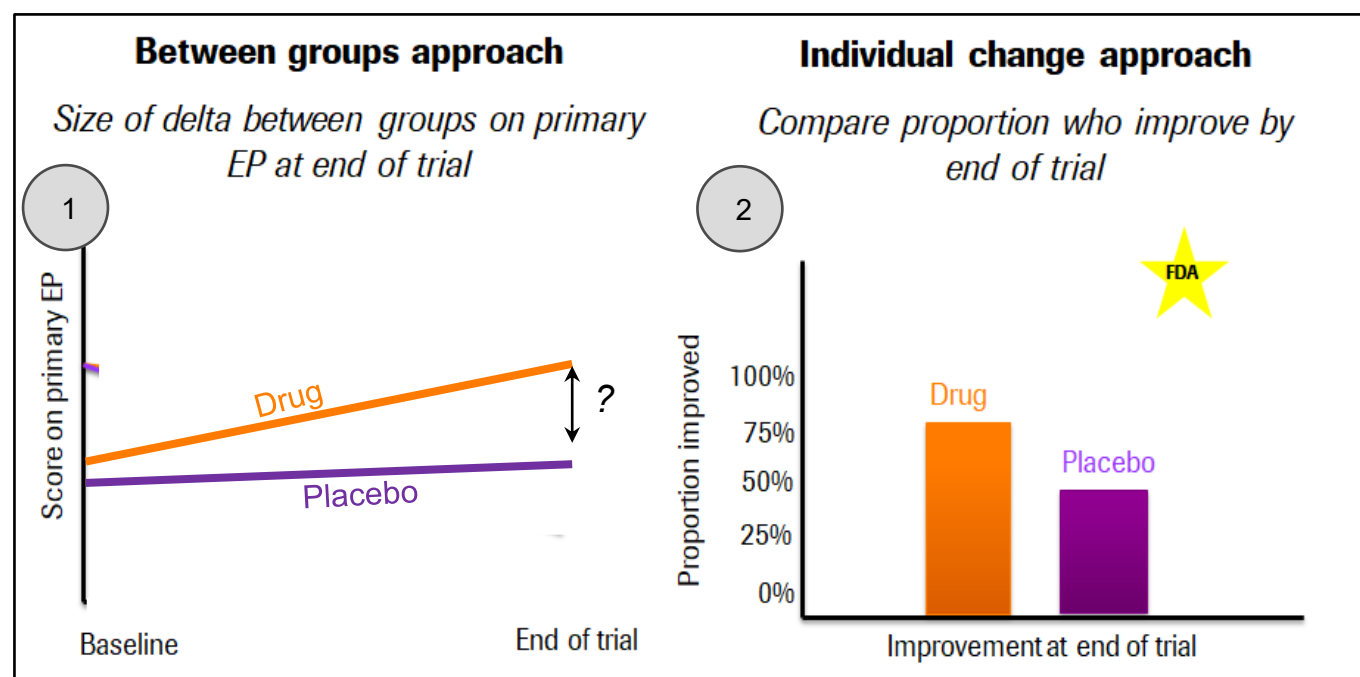
- **Approach 2 Advantage:** Clearly conveys how many patients in the study benefited from the drug, which is unclear in the between-groups approach.
- **Threshold Determination:** Common methods for determining an appropriate threshold for meaningful improvement or decline are covered in the [FDA PFDD workshop documents](#).

## MCID

Between-groups approach

## within-patient MCT

Individual change approach



How do you prepare for this within-patient MCTs in a Ph3 when there is no established threshold for your COA of interest?

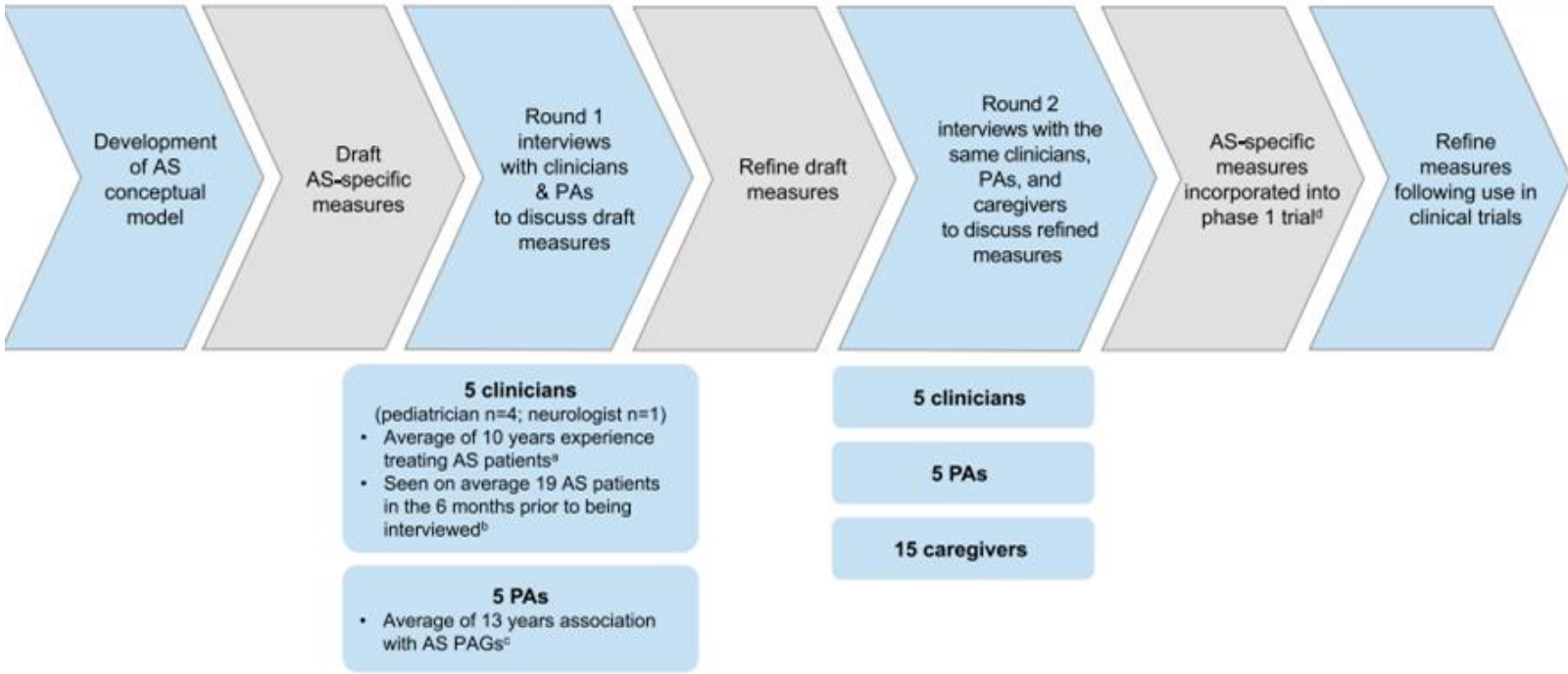
# Dual purpose global impressions: A Holistic Approach to AS Assessment

- Development of the Clinician and Caregiver global impressions (**SAS-CGI** and **CASS** respectively)
- Purpose: Used to capture broader AS symptoms AND for use as an anchor to calculate within person MCT on the Bayley

These assess:

1. Communication (expressive and receptive)
2. Cognition
3. AAC device usage
4. Motor skills (fine and gross)
5. Seizures
6. Sleep
7. Maladaptive Behaviours
8. Self-care
9. AS overall

A rigorous development process, consistent with FDA guidance, was followed to develop AS-specific measures for use in clinical trials



CASS

CASS – Impact

|                          |                          |                          |                          |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Not at all difficult     | A little difficult       | Somewhat difficult       | Quite difficult          | Very difficult           |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

CASS – Change

|                          |                          |                          |                          |                          |                          |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Very much improved       | Much improved            | Minimally improved       | No change                | Minimally worse          | Much worse               | Very much worse          |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Connor-Ahmad, S., Tjeertes, J., Chladek, M., Newton, L., Symonds, T., Clinch, S., Vincenzi, B. and McDougall, F., 2023. Developing Angelman syndrome-specific clinician-reported and caregiver-reported measures to support holistic, patient-centered drug development. *Orphanet Journal of Rare Diseases*, 18(1), p.156.  
Version 2 of the measures available on [eProvide here](#)

# Lessons learned

## Multiple qualitative insights are needed to inform a measurement strategy

### 01. Conceptual Model

- Develop/utilise existing disease-specific conceptual models **early in clinical development** to identify disease-defining domains.
- In heterogeneous populations, this may result in a large number of different domains (in AS -> 11 'disease defining' domains)

### 02. Patient-Centricity

- Prioritize affected disease domains to those **most meaningful to patients** and caregivers, determining whether they represent distal or proximal concepts.

### 03. Gap & History Analysis

- Assess **available measures through gap analyses** to gain confidence, and generate natural history data to track symptom severity, frequency, and trajectory over time.

### 04. Endpoint Construction

- Optimize primary endpoints using **FDA Multiple Endpoint guidance**, weigh the pros and cons of different clinical scenarios, and actively integrate early health authority feedback.

Well designed qualitative research with patients/caregivers and HCPs informs/supports this step



# Key Takeaways

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 Multi-system diseases (like AS) require multi-domain endpoints to capture total treatment effect.
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 Required by regulators to demonstrate how meaningful aspects of health are identified, selected and prioritized, guiding domain selection and justifying COAs.
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# Acknowledgements

Siobhan Connor-Ahmad  
Fiona McDougall  
Tom Willgoss  
Krystian Przydzial  
Julian Tillman

Roche Angelman Syndrome team (past and present)

# BACKUP

# Assessing broader meaningful aspects of health

## Learnings / Considerations



### Utilizing Global Impression items

- Psychometric properties evaluating **validity** and **reliability** need to be explored within clinical trial settings
- How are items scores considered **meaningful**?
- **Specific age**-group items should be targeted (i.e. are they not suitable for children <1 year?)
- **Part of primary endpoint** or used as an **anchor-based** measurement for establishing meaningful change, via disease-specific Global Impression scales

### Types of Health Authority feedback to expect

- Are the COAs *really* measuring the **concepts of interest**?
- **Recall period** (i.e. 24hr / 7 days / 14 days etc)
  - Shorter recall = minimize memory bias but higher respondent burden
- **Validity and reliability (ie psychometric properties)** of COAs in this specific population
- What score change is **meaningful to patients and/or their families**?