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Boosting caregivers’ role in measuring the value of new treatments in rare diseases

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Patient-Centered Outcomes Research (PROQOL), Health Economics Clinical Trial Unit (URC-ECO), hôpital Hôtel-Dieu, AP-HP, Université Paris Cité

Past chair of the ISPOR COA SIG

Our panelists will present why it matters to measure caregiver's quality of life and burden in rare diseases in the context of HTA

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Terry Jo Bichell	PhD, MPH, Founder, and director of COMBINED Brain (The Consortium for Outcome Measures and Biomarkers for Neurodevelopmental Disorders), USA
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DISCLOSURE

Sanofi was the sponsor and provided content support for this Issue Panel; Medical writing and editorial assistance were provided by ICON.

Conflict-of-interest statement

Recent links with: Sanofi, Pfizer, Gilead, Boiron, ViiV, BMS, Novartis, AZ, Takeda, IQVIA, and ICON plc

CARE WORK = INVISIBLE LABOUR

PEOPLE want and need to be cared for and looked after. Functioning together in a society that is healthy, peaceful and worth living in should not be taken for granted. There is a lot of work involved, such as running a household, bringing up children, and caring for the sick and needy. All these activities have no commodity value because they do not produce tangible products. Therefore, in economics they are referred to as non–productive activities, colloquially they are considered invisible labour. A study by the charity Oxfam found that the value of unpaid domestic, care and welfare work alone is equivalent to about 11 trillion US dollars a year if it were paid at the minimum wage. This work is mainly performed by women.

In current scientific considerations, the entirety of paid and unpaid person–oriented care services is summarised in the English term care work, which is difficult to translate into German. The term focuses on the job responsibilities of the occupational activities. Furthermore, it emphasises that in most cases, where such work is provided as a financially remunerated service, it is precariously paid. Unpaid and paid care work are often intertwined. If there is a need for care in a family, for example due to the illness of an elderly person, it is often no longer possible for the person to be fully cared for by relatives. Then a solution must be pursued through paid care and nursing staff.

“Emotionally it’s very stressful, but sometimes it’s also beautiful.”

CARE–ARBEIT = UNSICHTBARE ARBEIT

“Emotional ist es sehr belastend, aber manchmal auch schön.”

MENSCHEN wollen und müssen ver– und umsorgt werden. Ein funktionierendes Miteinander in einer möglichst gesunden, friedlichen und lebenswerten Gesellschaft ist keine Selbstverständlichkeit. Dahinter steckt viel Arbeit, etwa die Haushaltsführung, die Erziehung von Kindern, die Pflege und Betreuung kranker und hilfsbedürftiger Menschen.
All diese Tätigkeiten haben keinen Warenwert, weil durch sie keine greifbaren Produkte erzeugt werden. Daher werden sie in der Ökonomie als nicht produktive Tätigkeiten bezeichnet, umgangssprachlich gelten sie als unsichtbare Arbeit. In einer Studie der Wohltätigkeitsorganisation Oxfam wurde festgestellt, dass allein der Wert der nicht bezahlten Haus–, Pflege– und Fürsorgearbeit etwa 11 Billionen US–Dollar pro Jahr entspricht, würde sie mit dem Mindestlohn bezahlt. Diese Arbeit wird hauptsächlich von Frauen erbracht.

In aktuellen wissenschaftlichen Betrachtungen wird die Gesamtheit der bezahlten und unbezahlten personenorientierten Versorgungsleistungen im englischen Begriff Care–Arbeit zusammengefasst, der sich schlecht übersetzen lässt. Der Begriff stellt die Arbeitsinhalte der Tätigkeiten in den Mittelpunkt. Darüber hinaus betont er, dass diese Arbeiten, wo sie als finanziell entlohnte Dienstleistungen erbracht werden, zumeist prekär bezahlt sind. Oft greifen unbezahlte und bezahlte Care–Arbeiten ineinander. Kommt es in einer Familie zu einem Betreuungsfall, etwa durch Erkrankung eines älteren Menschen, kann die Person oft nicht mehr vollständig durch die Angehörigen versorgt werden. Dann muss eine Lösung durch bezahlte Betreuungs– und Pflegekräfte gesucht werden.

The impact/burden of a disease of a child/adult on the quality of life of caregivers is obvious

Taking care of his/her mother having Alzheimer: emotional, physical, (sometimes) financial burden of the caregiver, that may lead to exhaustion

Taking care of his/her child having a severe genetic disease: just the fear of the next crisis may have a great impact on emotional, physical, social functions, sleep…

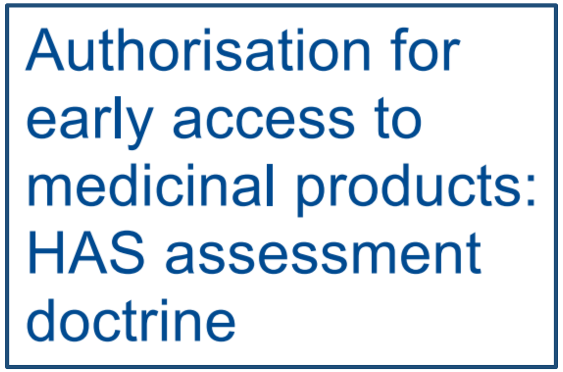
Hence, an improvement of a severe disease that would also translate in a burden relief of the caregivers is informative:

- It confirms the endpoints of the disease
- A caregiver’s burden relief has an economic value

Is there a place for valuing caregiver burden in HTA
e.g. in early access of drugs in rare diseases?

Transparency Committee doctrine

Principles of medicinal product assessments and appraisal for reimbursement purposes



Authorisation for early access to medicinal products: HAS assessment doctrine

HAUTE AUTORITÉ DE SANTÉ

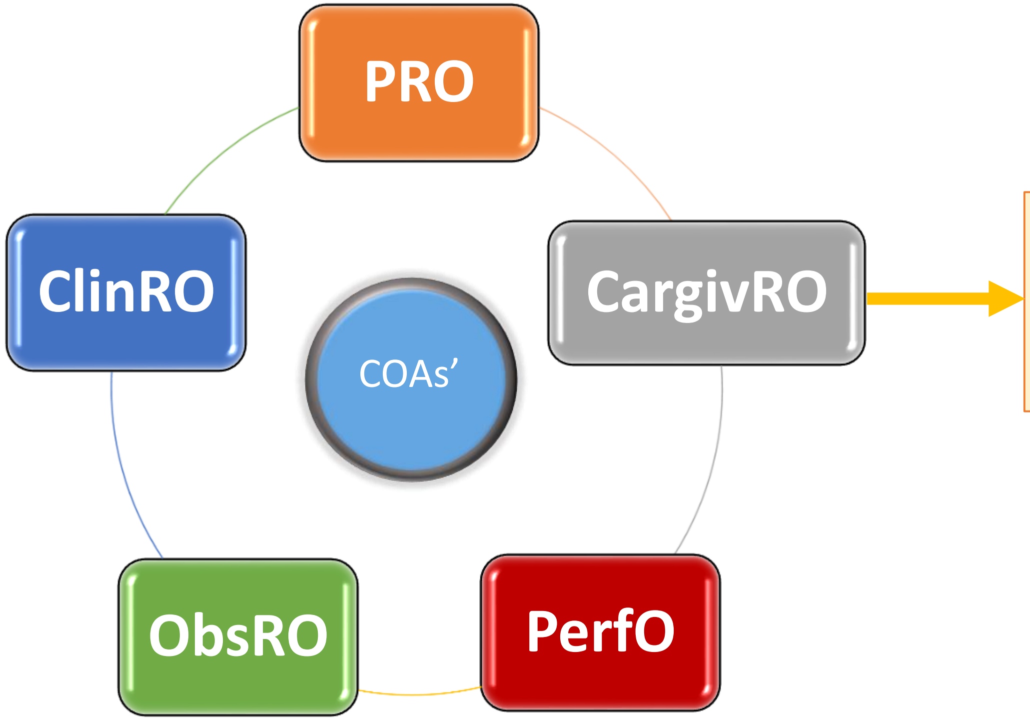
Early access authorisation is an exceptional derogation-based scheme enabling the early availability … of a medicinal product indicated for a severe, **rare** or incapacitating disease …

The medicinal product …, capable of contributing major progress … either in terms of efficacy (including **quality of life**), safety, or:

- **Simplify the care pathway or have a positive organizational impact (e.g., hospital or non-hospital care pathway)**
- **Improve patients' quality of life (e.g., change from injectable administration to oral administration)**

https://www.has-sante.fr/upload/docs/application/pdf/2021-08/authorisation_for_early_access_to_medicinal_products_has_assessment_doctrine.pdf

Suggestion to add a new endpoint for the evaluation of health technologies?


PRO

ClinRO

CargivRO

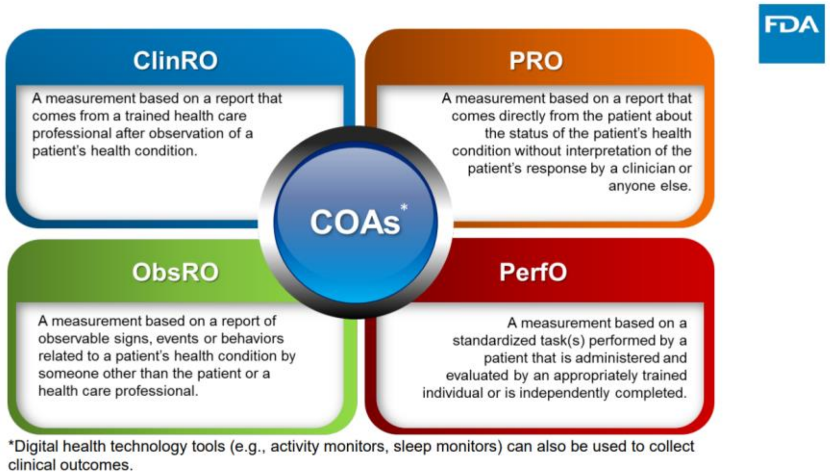
COAs'

ObsRO

PerfO

A measurement based on a report that comes directly from the caregiver about the caregiver's impact and burden on his/her own quality of life

https://www.fda.gov/about-fda/clinical-outcome-assessment-coa-frequently-asked-questions



ClinRO

A measurement based on a report that comes from a trained health care professional after observation of a patient's health condition.

PRO

A measurement based on a report that comes directly from the patient about the status of the patient's health condition without interpretation of the patient's response by a clinician or anyone else.

ObsRO

A measurement based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than the patient or a health care professional.

PerfO

A measurement based on a standardized task(s) performed by a patient that is administered and evaluated by an appropriately trained individual or is independently completed.

*Digital health technology tools (e.g., activity monitors, sleep monitors) can also be used to collect clinical outcomes.

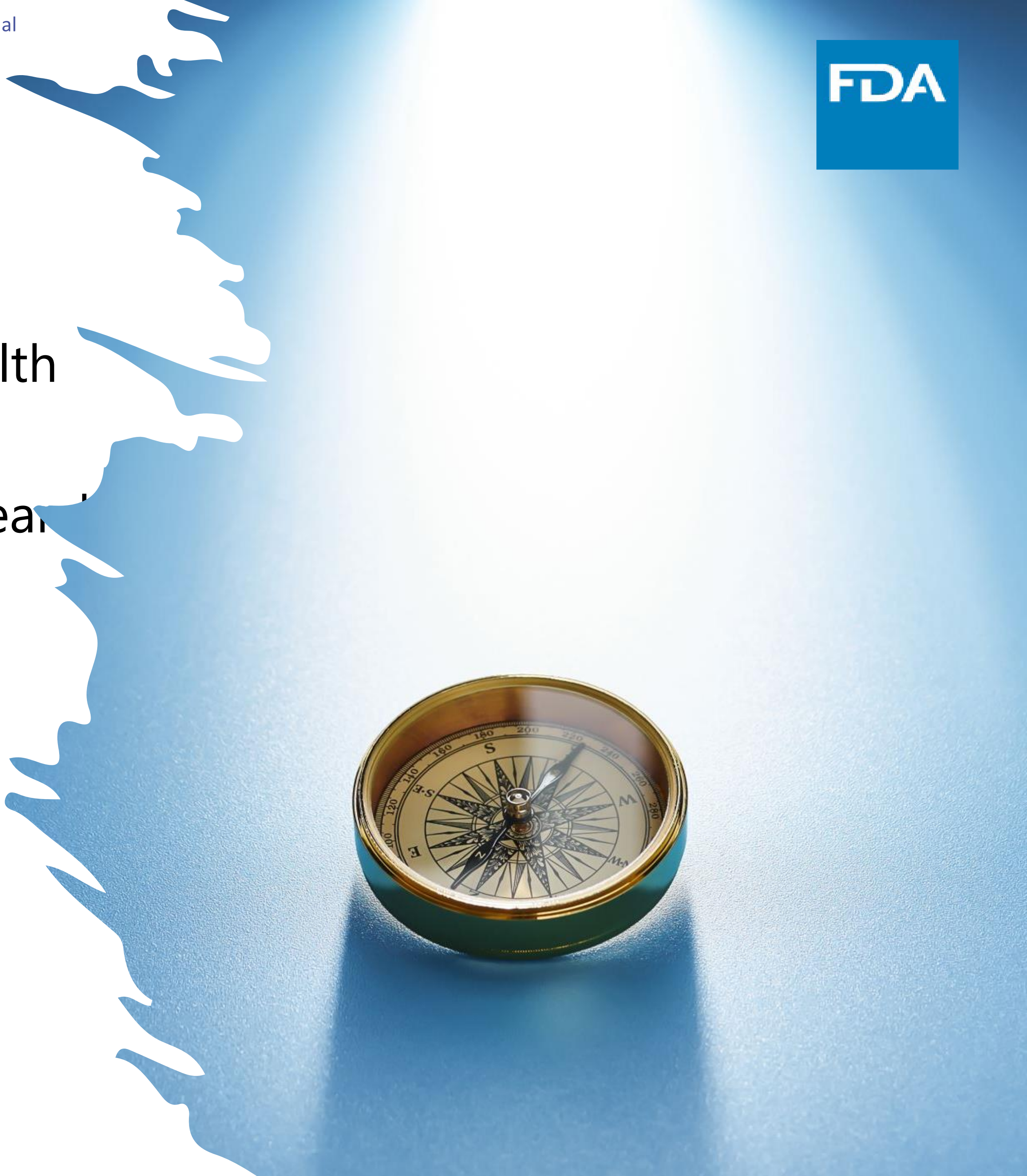
ENGAGING CAREGIVERS IN RARE DISEASE MEDICAL PRODUCT DEVELOPMENT: US REGULATORY PERSPECTIVE

Selena R. Daniels, PharmD, PhD
Team Leader, Division of Clinical Outcome Assessment
Office of Drug Evaluation Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Disclaimer

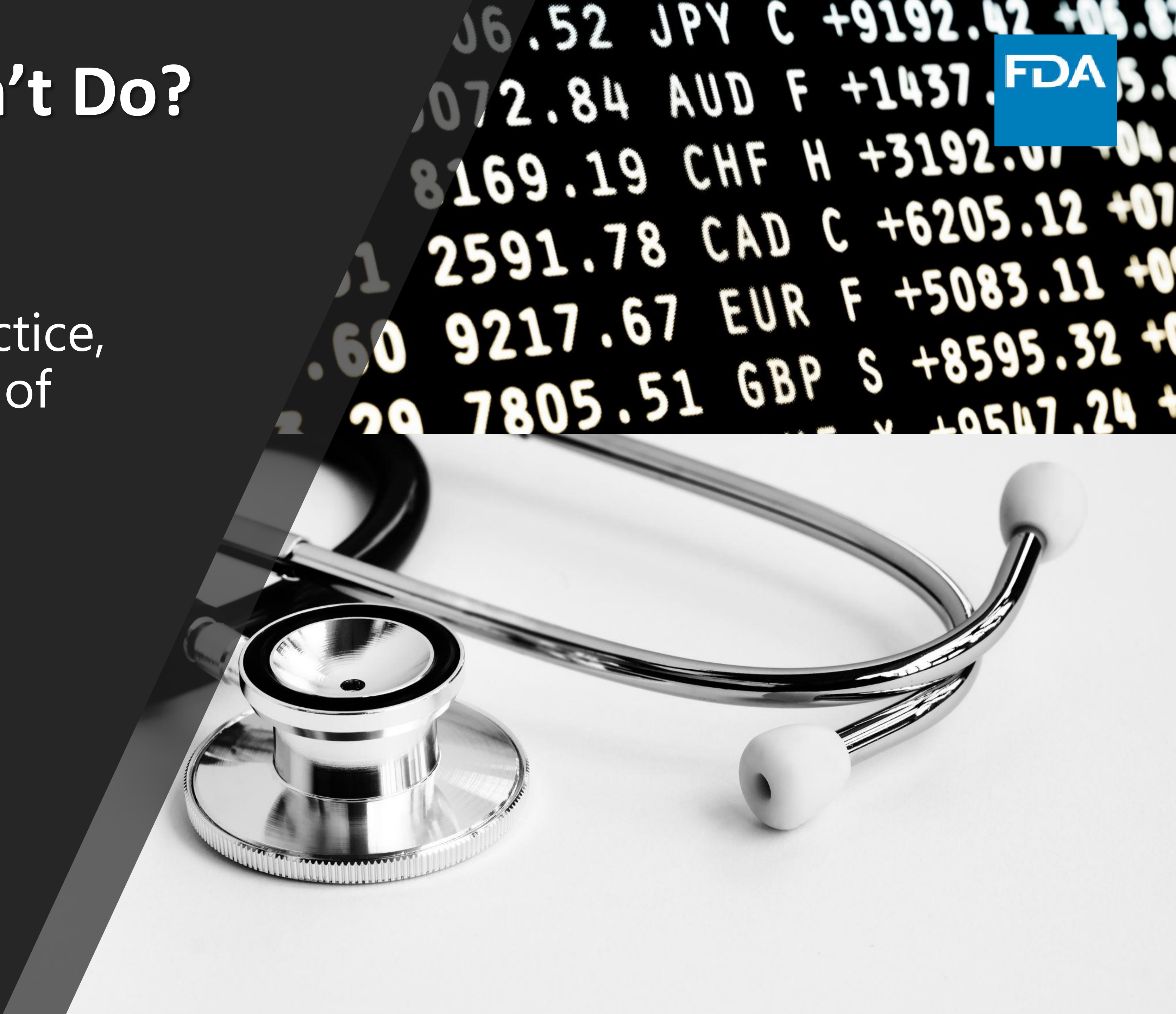
FDA: What We Do?

- Mission: Promote and protect public health
- FDA Center for Drug Evaluation and Resea (CDER) ensures the safety and efficacy of drugs



FDA: What We Don’t Do?

- Dictate medical practice, service, or the price of medical products



Our Ultimate Purpose: Understand Patients' Perspectives on Benefits and Risks

Clinical benefit: A ***positive clinically meaningful effect*** of an intervention, i.e., a positive effect on how an individual ***feels***, ***functions***, or ***survives***

- How long a patient lives
- How a patient feels or functions in daily life (includes both improvement as well as prevention/slowing decline)

Clinical outcome: An outcome that describes or reflects how an individual feels, functions or survives

- Assessed using clinical outcome assessments and/or digital health technology

Careful assessment of *patients' views on benefits and risks* are an *important part of regulatory decision-making*

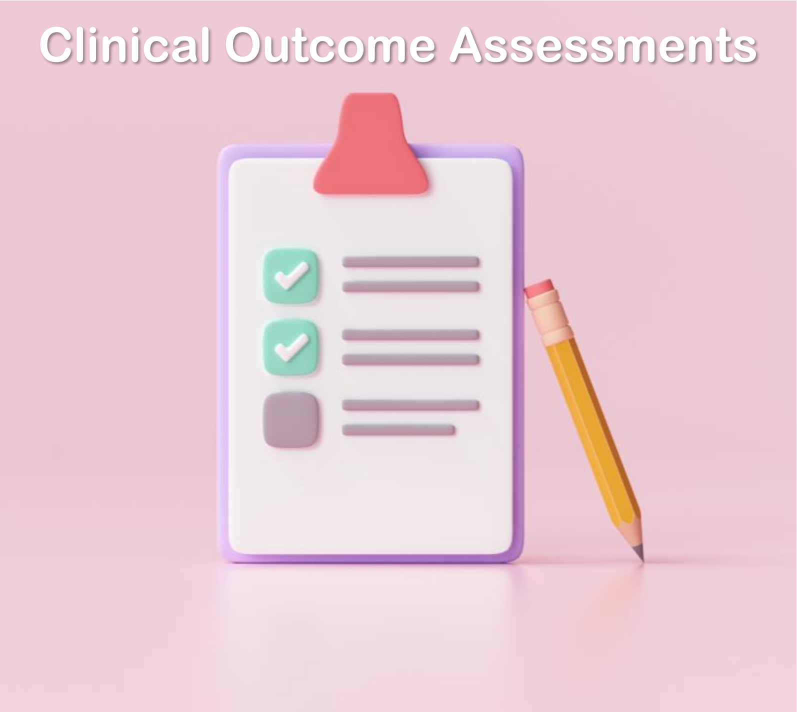
BEST Glossary: https://www.ncbi.nlm.nih.gov/books/NBK338448/

Determining Who Provides Patient Experience Data

Leveraging Caregiver Input to Inform Drug Development & Regulatory Decision-Making

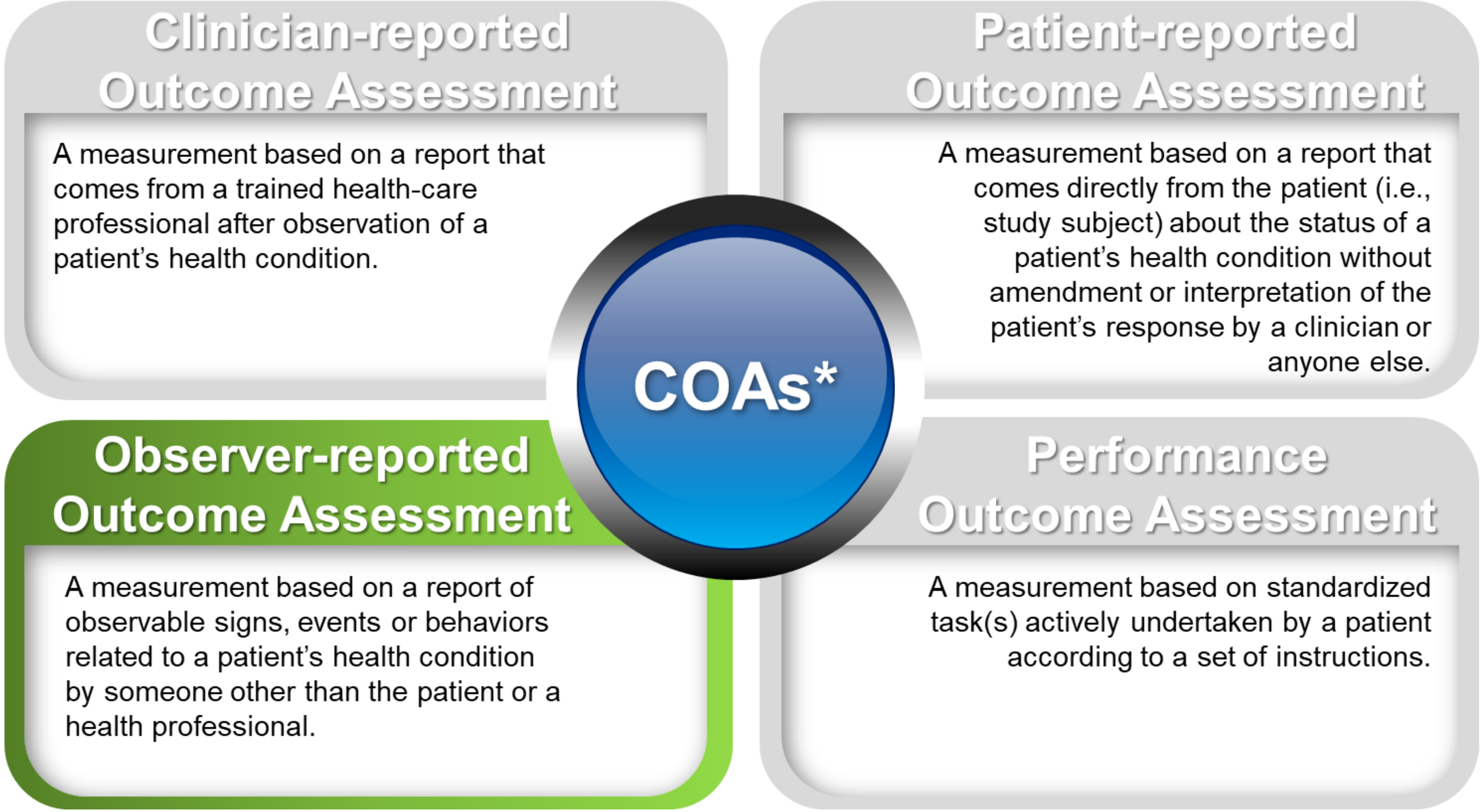

FDA PFDD Meetings


FDA Patient Listening Sessions


Clinical Outcome Assessments

Clinical Outcome Assessments (COAs)

COA: Assessment of a clinical outcome made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment



Clinician-reported Outcome Assessment

A measurement based on a report that comes from a trained health-care professional after observation of a patient’s health condition.

Patient-reported Outcome Assessment

A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient’s health condition without amendment or interpretation of the patient’s response by a clinician or anyone else.

Observer-reported Outcome Assessment

A measurement based on a report of observable signs, events or behaviors related to a patient’s health condition by someone other than the patient or a health professional.

Performance Outcome Assessment

A measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions.

*Digital health technology can also be used to collect health-care related data.

BEST Glossary: https://www.ncbi.nlm.nih.gov/books/NBK338448/

Case Example: Caregiver Input from FDA Patient Listening Session

pfic | ADVOCACY & RESOURCE NETWORK, INC.

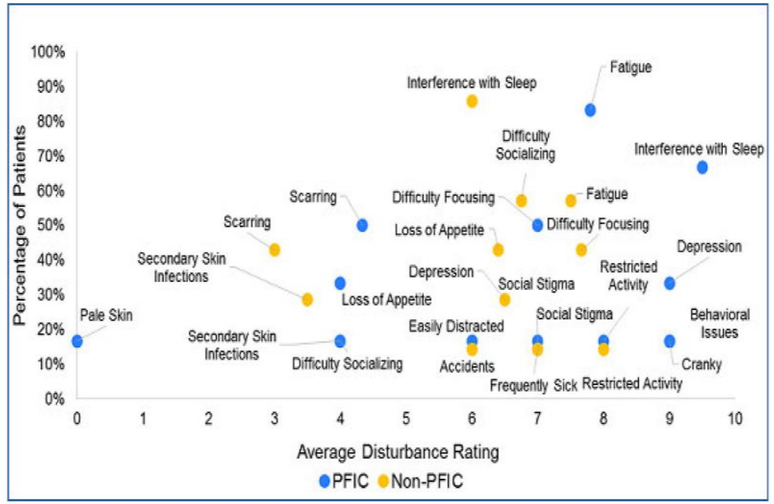
FDA LISTENING SESSION OVERVIEW

Patient & Family Testimonials -Progressive familial intrahepatic cholestasis (PFIC)

1. Tara Kearns: PFIC 3 mom, Road to Transplant and Life After
   - 1.1 Everyday life, how PFIC 3 impacts the life of an active 10 year old
   - 1.2 Discusses complications due to vitamin deficiency and immune suppression
2. Emily Ventura: PFIC 2 mom, Experience with PFIC 2, Complications Post Transplant
   - 2.1 Shares the uncertainty and ineffectiveness of current treatment options
   - 2.2 Discusses the recurrence of PFIC 2 disease post transplant, Allo-Immune BSEP Deficiency (AIBD)
3. Sharon Munn: PFIC 1 mom, Experience with PFIC 1, Complications Post Transplant
   - 3.1 Discusses the distress that PFIC has caused in family life and in childhood
   - 3.2 Shares the challenges that have occurred specifically related to PFIC 1 post transplant
4. Charmaine Gravener: PFIC 2 mom, Proof of hope in new therapies, Experience with IBAT inhibitors in trial
   - 4.1 Shares a closer look at pruritus and the impact on the child and family
   - 4.2 Shares her success story with current therapies that are in trial

Case Example:
Caregiver Input From ObsRO

- Progressive familial intrahepatic cholestasis (PFIC) is a rare, autosomal recessive genetic disorder
- Patient-focused evidence shows that **itching** is the most frequently reported and disturbing symptom
  - Itching received a mean disturbance rating of 6.3 (on a 0-10 scale)
  - PFIC patients and caregivers reported itching as the highest impact (7.8 on a 0-10 scale)



[Figure. Pruritus - Functional Impact Frequency vs. Average Disturbance (PFIC vs. non-PFIC)]

Source: 51st ESPGHAN Annual Meeting. Journal of Pediatric Gastroenterology and Nutrition 66():p 1-1177, April 2018. | DOI: 10.1097/MPG.0000000000002005

Case Example:
Caregiver Input from ObsRO

- Odevixibat was approved in 2021 for the treatment of pruritus in patients **ages 3-months and older** with PFIC
- **Observed scratching** was measured by an **ObsRO** assessment with **PRO** data as supportive

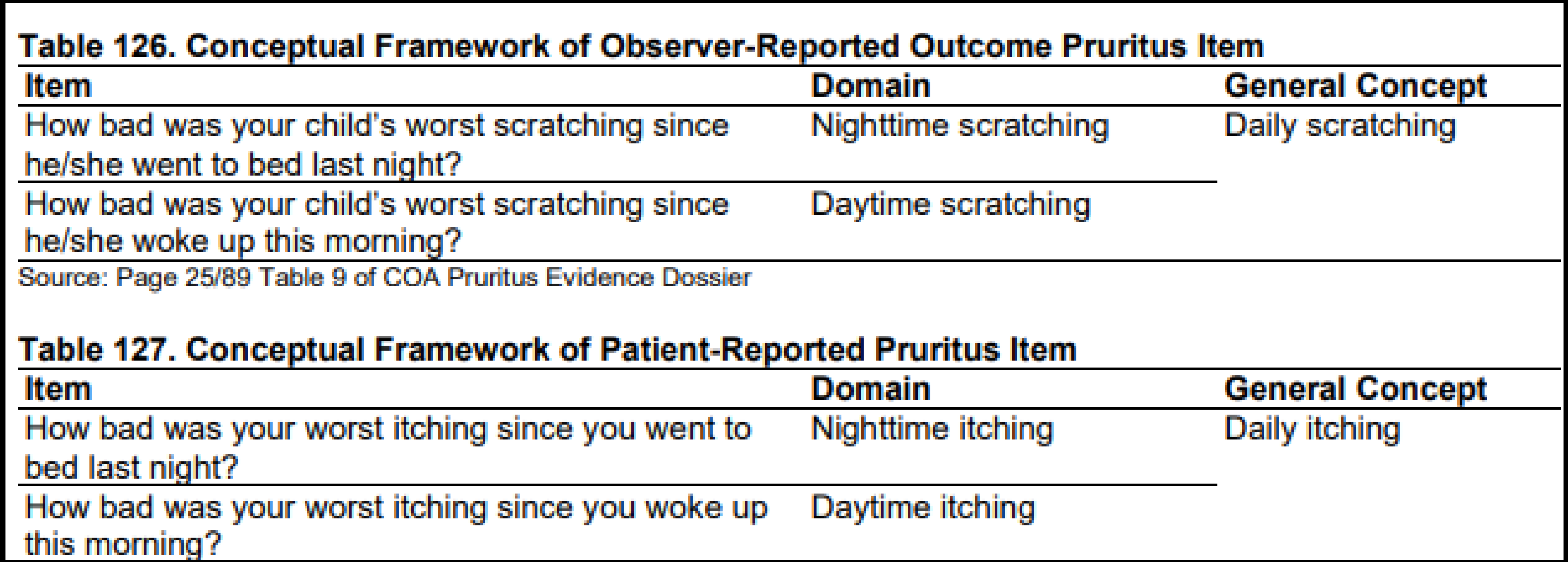


Table 126. Conceptual Framework of Observer-Reported Outcome Pruritus Item

Item	Domain	General Concept
How bad was your child's worst scratching since he/she went to bed last night?	Nighttime scratching	Daily scratching
How bad was your child's worst scratching since he/she woke up this morning?	Daytime scratching	

Source: Page 25/89 Table 9 of COA Pruritus Evidence Dossier

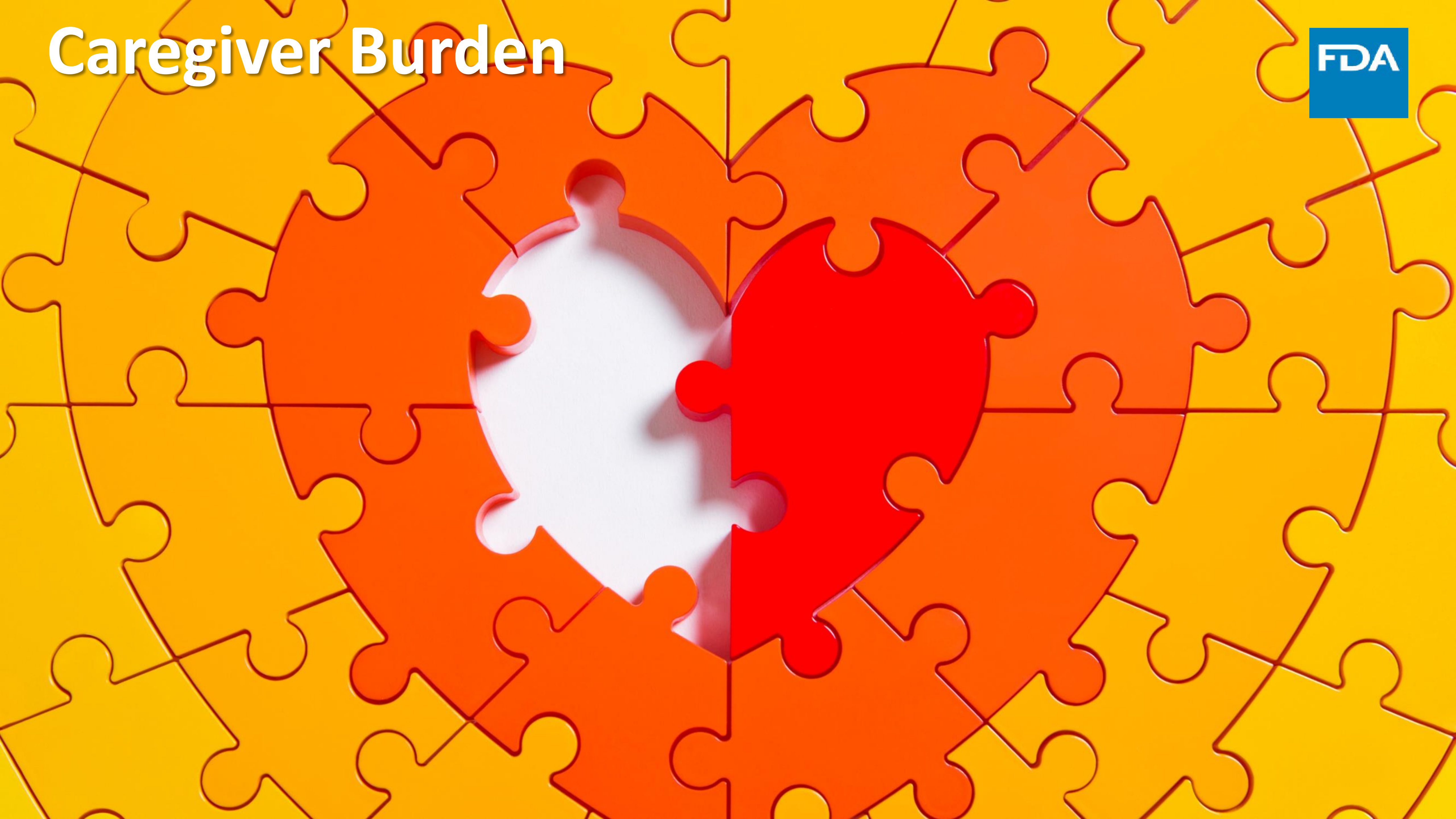
Table 127. Conceptual Framework of Patient-Reported Pruritus Item

Item	Domain	General Concept
How bad was your worst itching since you went to bed last night?	Nighttime itching	Daily itching
How bad was your worst itching since you woke up this morning?	Daytime itching	

Source: Center for Drug Evaluation and Research Integrated Review

For the public review, see: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215498Orig1s000IntegratedR.pdf

Caregiver Burden



Summary

Engaging both patients and caregivers enhances FDA's ability to hear, understand, and integrate their unique and important perspectives to help advance and improve public health.

Concerted, multi-stakeholder, multi-disciplinary approach needed for rare disease medical product development.

Patient-Focused Drug Development

FDA Wants To Hear From Patients & Caregivers

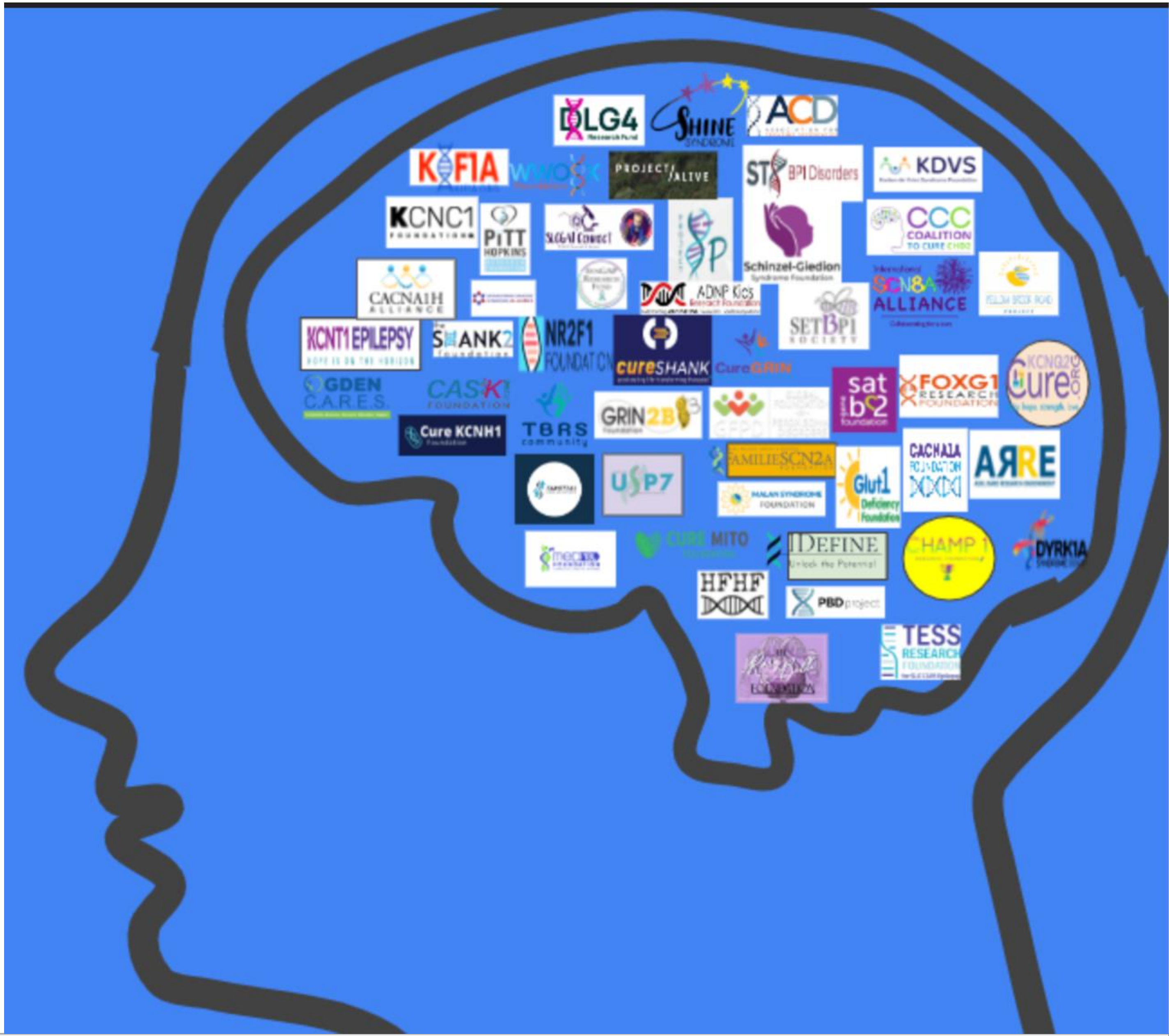
U.S. FOOD & DRUG ADMINISTRATION

COMBINEDBrain

Consortium for Outcome Measures and Biomarkers for Neurodevelopmental Disorders

Terry Jo Bichell, MPH, PhD

Boosting caregivers’ role in measuring the value of new treatments in rare diseases: Caregiver’s Perspective



Credentials

PhD, Neuroscience

MPH, Maternal and Child Health

CNM, Nurse-Midwife

Director, COMBINEDBrain

Mother, Adult Son with Angelman syndrome

Relevant Financial Disclosures

Hoffman-LaRoche Pharmaceuticals

Angelman patient advisory board, Honoraria

Caregivers provide a voice for the voiceless

Genetic neurodevelopmental disorders

Caregivers must speak for non-speaking patients

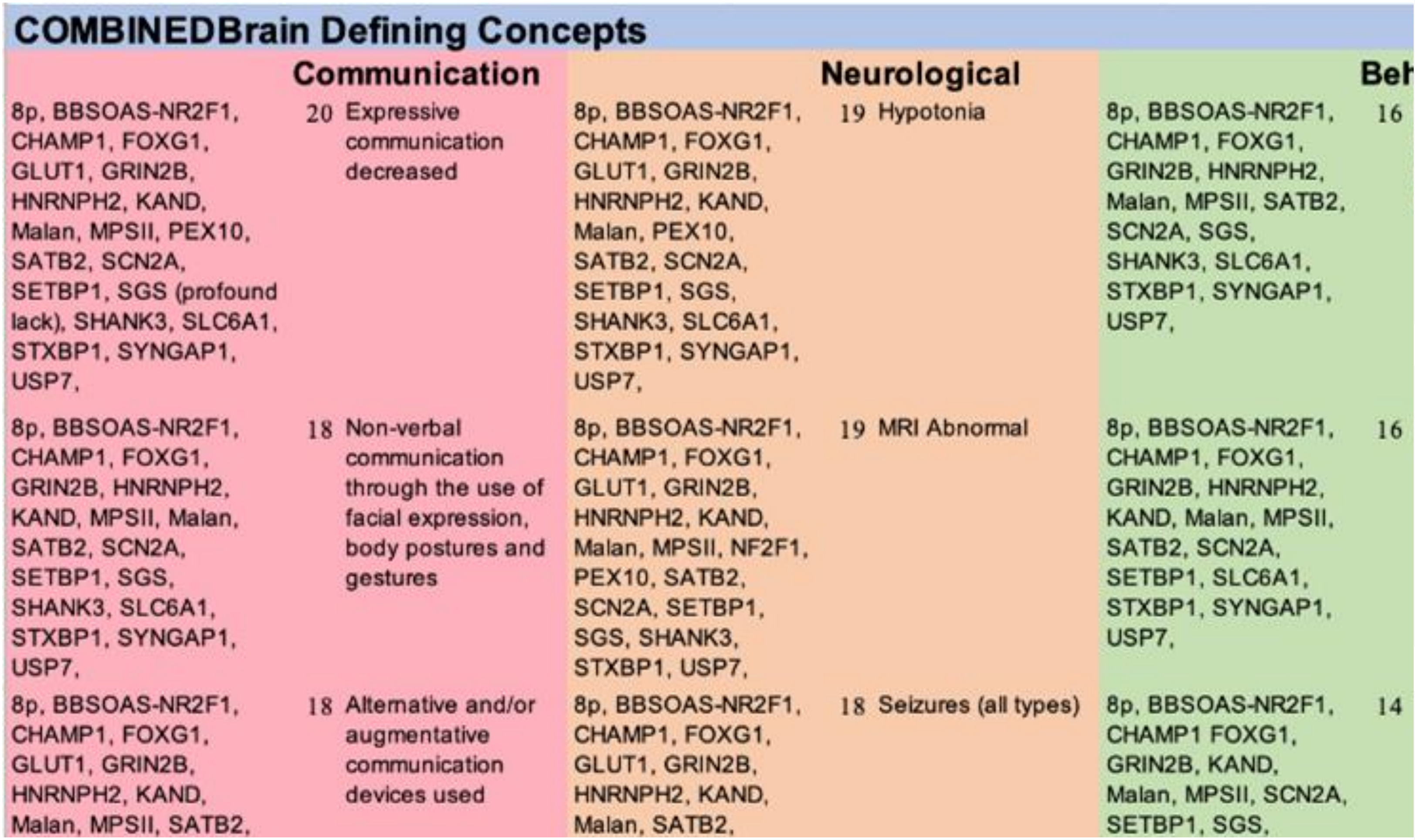
Clinician evaluations limited in scope

Caregivers can describe full lived experience of patients

FOXG1 syndrome, medically-induced coma, with permission, N. Fitter, 2023

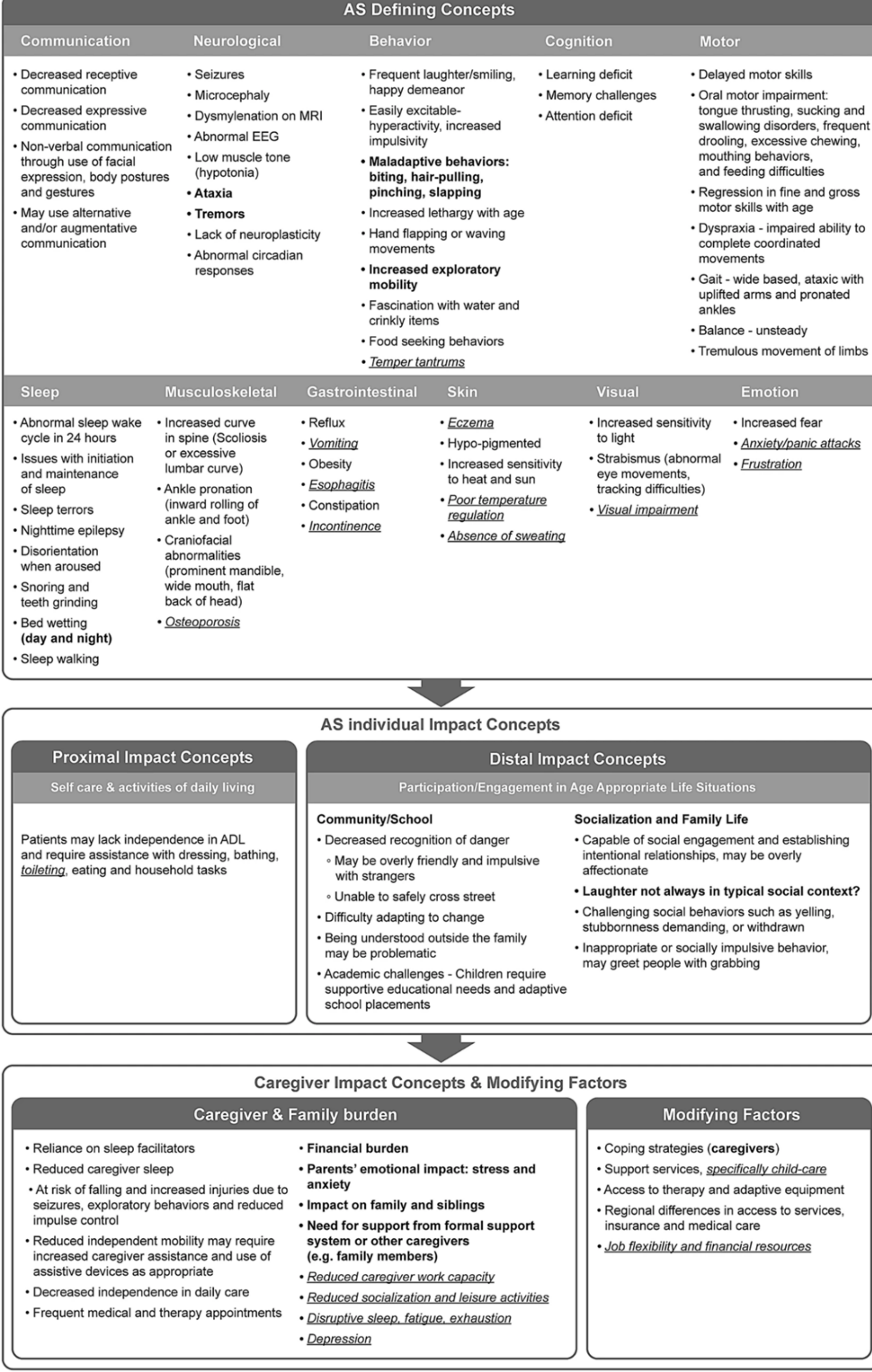
Disease Concept Maps

Lived experience as described by patients and caregivers builds a full model of disease



COMBINEDBrain Defining Concepts

		Communication			Neurological		Beh
8p, BBSOAS-NR2F1, CHAMP1, FOXG1, GLUT1, GRIN2B, HNRNPH2, KAND, Malan, MPSII, PEX10, SATB2, SCN2A, SETBP1, SGS (profound lack), SHANK3, SLC6A1, STXBP1, SYNGAP1, USP7,	20	Expressive communication decreased	8p, BBSOAS-NR2F1, CHAMP1, FOXG1, GLUT1, GRIN2B, HNRNPH2, KAND, Malan, PEX10, SATB2, SCN2A, SETBP1, SGS, SHANK3, SLC6A1, STXBP1, SYNGAP1, USP7,	19	Hypotonia	8p, BBSOAS-NR2F1, CHAMP1, FOXG1, GRIN2B, HNRNPH2, Malan, MPSII, SATB2, SCN2A, SGS, SHANK3, SLC6A1, STXBP1, SYNGAP1, USP7,	16
8p, BBSOAS-NR2F1, CHAMP1, FOXG1, GRIN2B, HNRNPH2, KAND, MPSII, Malan, SATB2, SCN2A, SETBP1, SGS, SHANK3, SLC6A1, STXBP1, SYNGAP1, USP7,	18	Non-verbal communication through the use of facial expression, body postures and gestures	8p, BBSOAS-NR2F1, CHAMP1, FOXG1, GLUT1, GRIN2B, HNRNPH2, KAND, Malan, MPSII, NF2F1, PEX10, SATB2, SCN2A, SETBP1, SGS, SHANK3, STXBP1, USP7,	19	MRI Abnormal	8p, BBSOAS-NR2F1, CHAMP1, FOXG1, GRIN2B, HNRNPH2, KAND, Malan, MPSII, SATB2, SCN2A, SETBP1, SLC6A1, STXBP1, SYNGAP1, USP7,	16
8p, BBSOAS-NR2F1, CHAMP1, FOXG1, GLUT1, GRIN2B, HNRNPH2, KAND, Malan, MPSII, SATB2,	18	Alternative and/or augmentative communication devices used	8p, BBSOAS-NR2F1, CHAMP1, FOXG1, GLUT1, GRIN2B, HNRNPH2, KAND, Malan, SATB2,	18	Seizures (all types)	8p, BBSOAS-NR2F1, CHAMP1 FOXG1, GRIN2B, KAND, Malan, MPSII, SCN2A, SETBP1, SGS,	14



AS Defining Concepts

Communication
- Decreased receptive communication
- Decreased expressive communication
- Non-verbal communication through use of facial expression, body postures and gestures
- May use alternative and/or augmentative communication

Neurological
- Seizures
- Microcephaly
- Dysmylenation on MRI
- Abnormal EEG
- Low muscle tone (hypotonia)
- **Ataxia**
- **Tremors**
- Lack of neuroplasticity
- Abnormal circadian responses

Behavior
- Frequent laughter/smiling, happy demeanor
- Easily excitable- hyperactivity, increased impulsivity
- **Maladaptive behaviors: biting, hair-pulling, pinching, slapping**
- Increased lethargy with age
- Hand flapping or waving movements
- **Increased exploratory mobility**
- Fascination with water and crinkly items
- Food seeking behaviors
- *Temper tantrums*

Cognition
- Learning deficit
- Memory challenges
- Attention deficit

Motor
- Delayed motor skills
- Oral motor impairment: tongue thrusting, sucking and swallowing disorders, frequent drooling, excessive chewing, mouthing behaviors, and feeding difficulties
- Regression in fine and gross motor skills with age
- Dyspraxia - impaired ability to complete coordinated movements
- Gait - wide based, ataxic with uplifted arms and pronated ankles
- Balance - unsteady
- Tremulous movement of limbs

Sleep
- Abnormal sleep wake cycle in 24 hours
- Issues with initiation and maintenance of sleep
- Sleep terrors
- Nighttime epilepsy
- Disorientation when aroused
- Snoring and teeth grinding
- Bed wetting **(day and night)**
- Sleep walking

Musculoskeletal
- Increased curve in spine (Scoliosis or excessive lumbar curve)
- Ankle pronation (inward rolling of ankle and foot)
- Craniofacial abnormalities (prominent mandible, wide mouth, flat back of head)
- *Osteoporosis*

Gastrointestinal
- Reflux
- *Vomiting*
- Obesity
- *Esophagitis*
- Constipation
- *Incontinence*

Skin
- *Eczema*
- Hypo-pigmented
- Increased sensitivity to heat and sun
- *Poor temperature regulation*
- *Absence of sweating*

Visual
- Increased sensitivity to light
- Strabismus (abnormal eye movements, tracking difficulties)
- *Visual impairment*

Emotion
- Increased fear
- *Anxiety/panic attacks*
- *Frustration*

AS individual Impact Concepts

Proximal Impact Concepts

Self care & activities of daily living

Patients may lack independence in ADL and require assistance with dressing, bathing, *toileting*, eating and household tasks

Distal Impact Concepts

Participation/Engagement in Age Appropriate Life Situations

Community/School
- Decreased recognition of danger
  - May be overly friendly and impulsive with strangers
  - Unable to safely cross street
- Difficulty adapting to change
- Being understood outside the family may be problematic
- Academic challenges - Children require supportive educational needs and adaptive school placements

Socialization and Family Life
- Capable of social engagement and establishing intentional relationships, may be overly affectionate
- **Laughter not always in typical social context?**
- Challenging social behaviors such as yelling, stubbornness demanding, or withdrawn
- Inappropriate or socially impulsive behavior, may greet people with grabbing

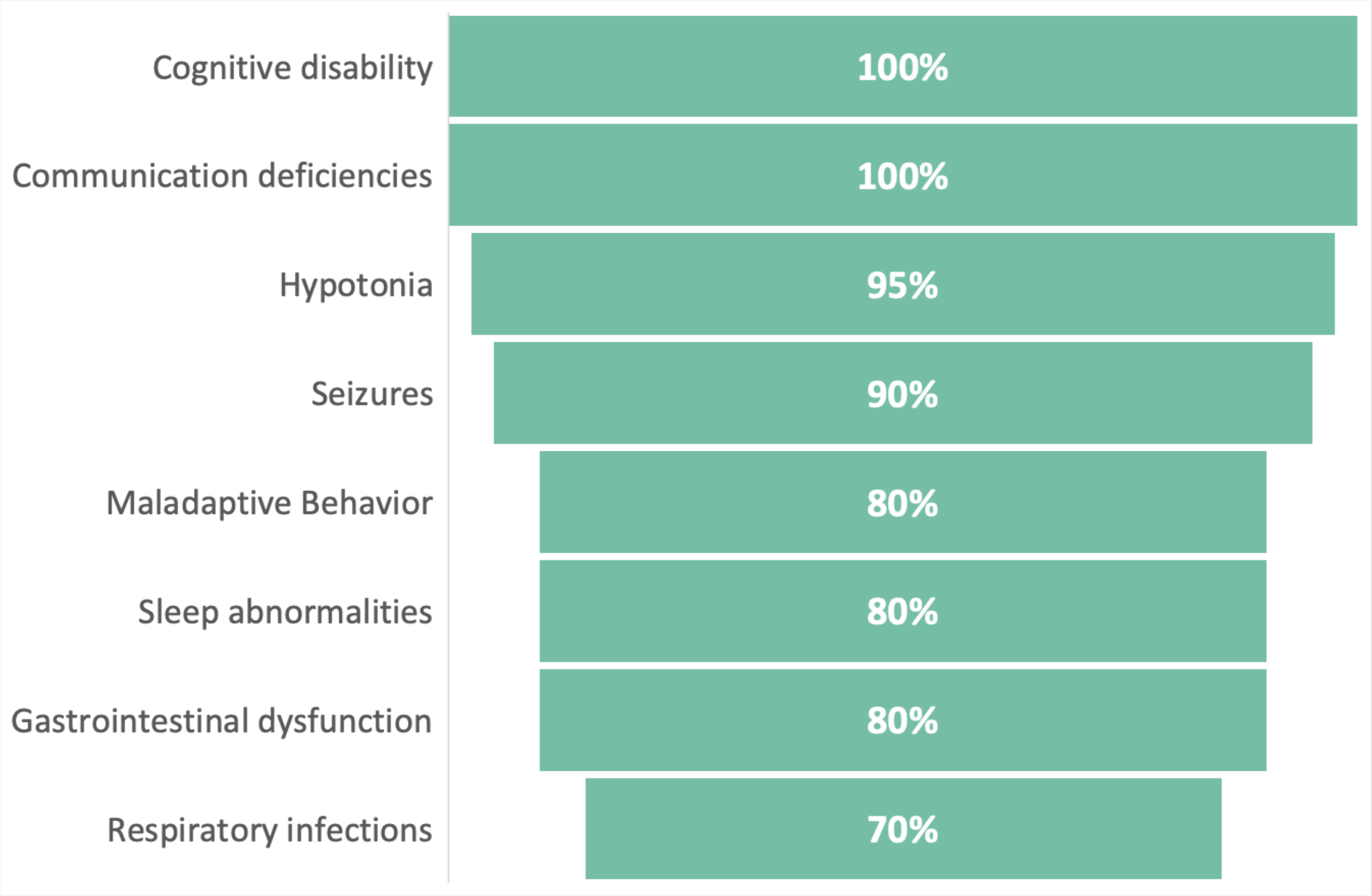
Caregiver Impact Concepts & Modifying Factors

Caregiver & Family burden
- Reliance on sleep facilitators
- Reduced caregiver sleep
- At risk of falling and increased injuries due to seizures, exploratory behaviors and reduced impulse control
- Reduced independent mobility may require increased caregiver assistance and use of assistive devices as appropriate
- Decreased independence in daily care
- Frequent medical and therapy appointments
- **Financial burden**
- **Parents' emotional impact: stress and anxiety**
- **Impact on family and siblings**
- **Need for support from formal support system or other caregivers (e.g. family members)**
- *Reduced caregiver work capacity*
- *Reduced socialization and leisure activities*
- *Disruptive sleep, fatigue, exhaustion*
- *Depression*

Modifying Factors
- Coping strategies (**caregivers**)
- Support services, *specifically child-care*
- Access to therapy and adaptive equipment
- Regional differences in access to services, insurance and medical care
- *Job flexibility and financial resources*

Willgoss et al (2020), Measuring What Matters to Individuals with Angelman syndrome.

Caregiver experience reveals unexpected burdens



SCN2A mutation, with permission, L. Myer, 2023

Caregiver involvement in development of meaningful endpoints

Communication abilities vs. seizures

example: Angelman syndrome

Observer-Reported Communication Abilities
expanded to 12 other neurodevelopmental disorders

ORCA

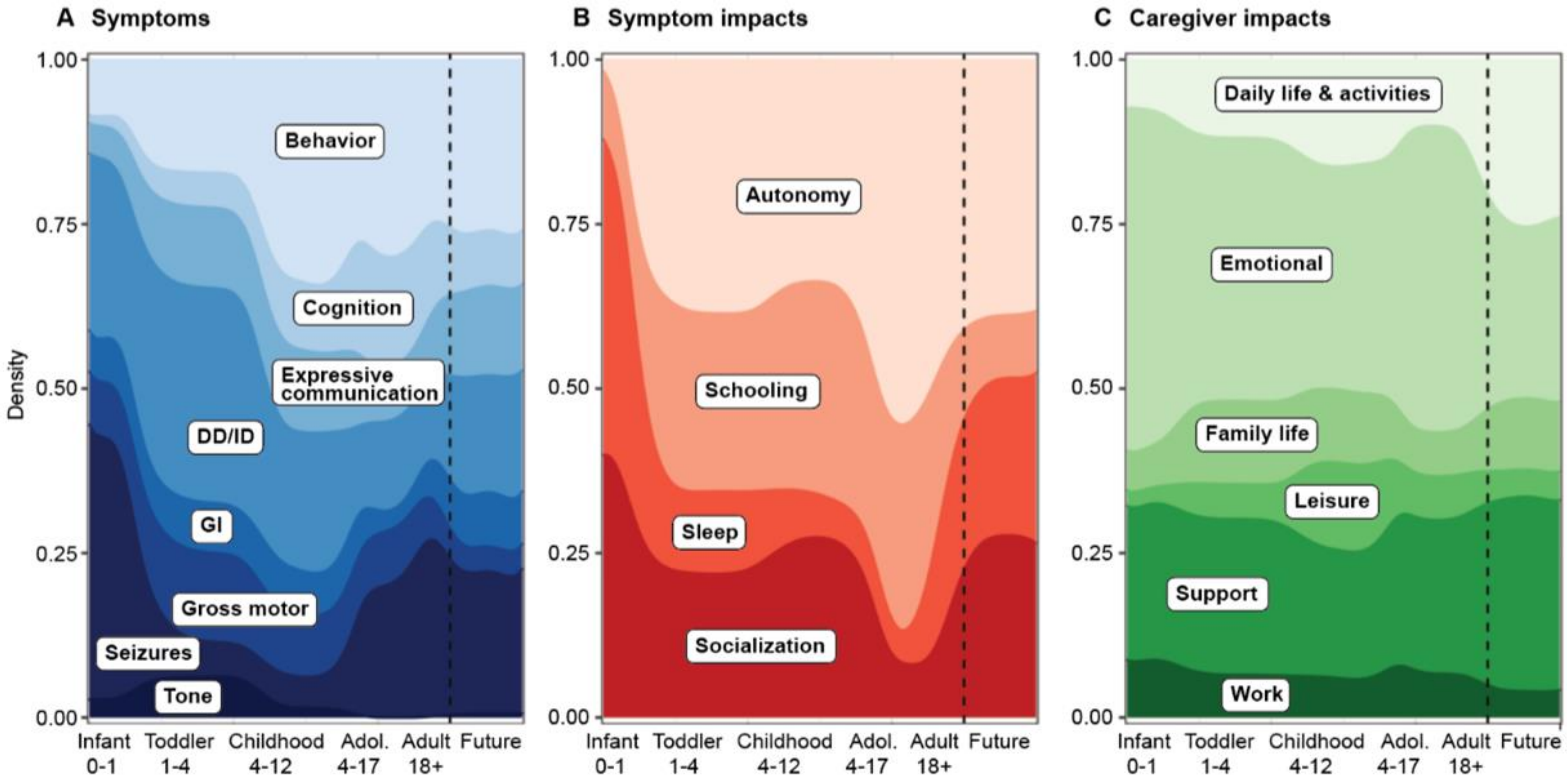
Observer-Reported Communication Ability Measure

Independent toileting abilities

example: Hunter syndrome

expanded to
Observer-Reported Toileting Abilities Survey

Patient and caregiver experience changes over the lifespan



www.COMBINEDBrain.org

Sullivan et al (2023), A disease concept model for STXBP1

Caregiver involvement in regulatory interactions

Example caregiver's report on patient experience: Neimann-Pick (ASMD)

Leadership of the National Niemann-Pick Disease Foundation and several members of the Niemann-Pick disease community met with members of the FDA in a "Listening Session"

Objective to discuss the complex nature of ASMD or Niemann-Pick types A and B and provide insight into how these complexities impact efforts in both clinical research and patient management.

Parents described how ASMD affected their children, and many spoke to the ways that enlarged abdominal organs led to pain, vomiting, eating difficulties, and falls:

"Parents were clear that there is significant unmet need for effective therapy, and while most reported improvements in systemic symptoms with olipudase therapy, families acknowledged that treatments for the neurologic manifestations remain an area of unmet need"

The review team concluded that, although there were serious IARS, they are self-evident to patients and reversible with treatment discontinuation, such that clear labeling would be sufficient to support doctors and patients in making informed, individualized treatment decisions.

- Every day she said, yes, my belly hurts, I have pain"
- "He was hooked up to feeding pumps, because the pressure that was being put on his stomach, he was only able to tolerate small volumes at a time"
- "Due to the bigger belly, she had some stability problems and she really fell a lot"
- "He would vomit upwards of five times a day"
- "After he was finished eating, he would throw up, which it makes sense now, with everything being so enlarged"
- "No child wants to be throwing up five times a day"

Niemann-Pick Disease Alliance webinar May 12, 2022, "Patient Reported Outcomes – Pediatric Experience with Olipudase alfa." (Cowie et al. 2022)
Structured interviews were conducted with ten caregivers in February of 2022.

Caregiver involvement in regulatory interactions

Example caregiver’s report on patient experience: Neimann-Pick (ASMD) – FDA listening session

Leadership of the National Niemann-Pick Disease Foundation and several members of the Niemann-Pick disease community met with members of the FDA in a “Listening Session”

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FDA Listening Session

Parents described how ASMD affected their children, and many spoke to the ways that enlarged abdominal organs led to pain, vomiting, eating difficulties, and falls

“Parents were clear that there is significant unmet need for effective therapy, and while most reported improvements in systemic symptoms with olipudase therapy, families acknowledged that treatments for the neurologic manifestations remain an area of unmet need”

The review team concluded that, although there were serious IARS, they are self-evident to patients and reversible with treatment discontinuation, such that clear labelling would be sufficient to support doctors and patients in making informed, individualized treatment decisions.

Accessed at: https://nnpdf.org/wp-content/uploads/2021/06/NNPDF-FDA-Listening-Session-SUMMARY-04-26-2021.pdf

Patient Reported Outcomes - Paediatric Experience with Olipudase alfa – INPDA, NNPDF, INPDR and NP-UK

"He was hooked up to feeding pumps, because the pressure that was being put on his stomach, he was only able to tolerate small volumes at a time"

- caregiver of pediatric ASMD patient

Every day she said, yes, my belly hurts, I have pain"

– caregiver of pediatric ASMD patient

"Due to the bigger belly, she had some stability problems and she really fell a lot"

– caregiver of pediatric ASMD patient

"He would vomit upwards of five times a day"

- caregiver of pediatric ASMD patient

"After he was finished eating, he would throw up, which it makes sense now, with everything being so enlarged"

- caregiver of pediatric ASMD patient

"No child wants to be throwing up five times a day"

- caregiver of pediatric ASMD patient

Niemann-Pick Disease Alliance webinar May 12, 2022, "Patient Reported Outcomes – Pediatric Experience with Olipudase alfa." (Cowie et al. 2022)
Structured interviews were conducted with ten caregivers in February of 2022.

Caregiver’s report on caregiver’s own experience as endpoint

Qualitative interviews of change

Quantitative measures in caregiver

Missed work days
Parental stress index
Support hours required
Sleep measures

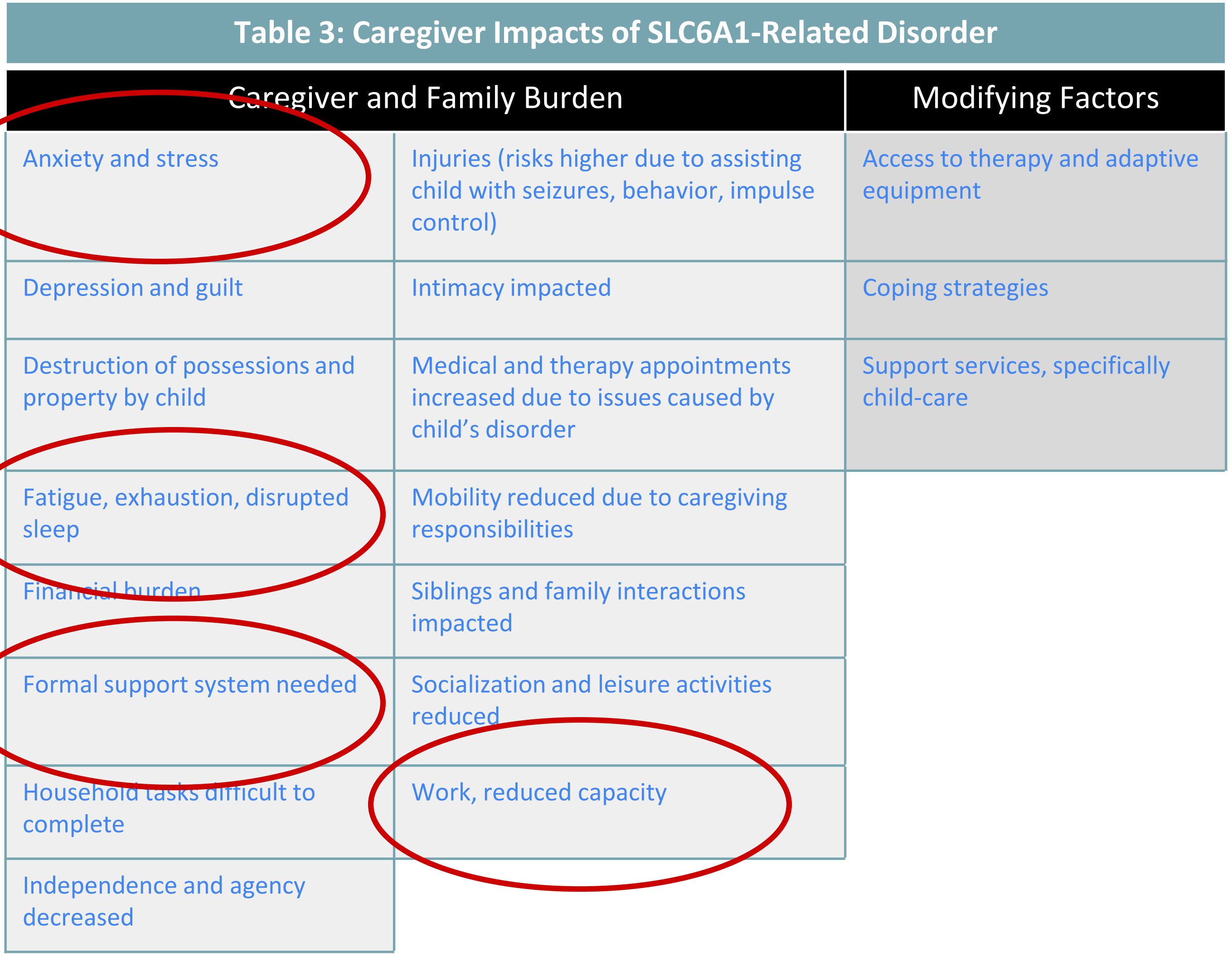


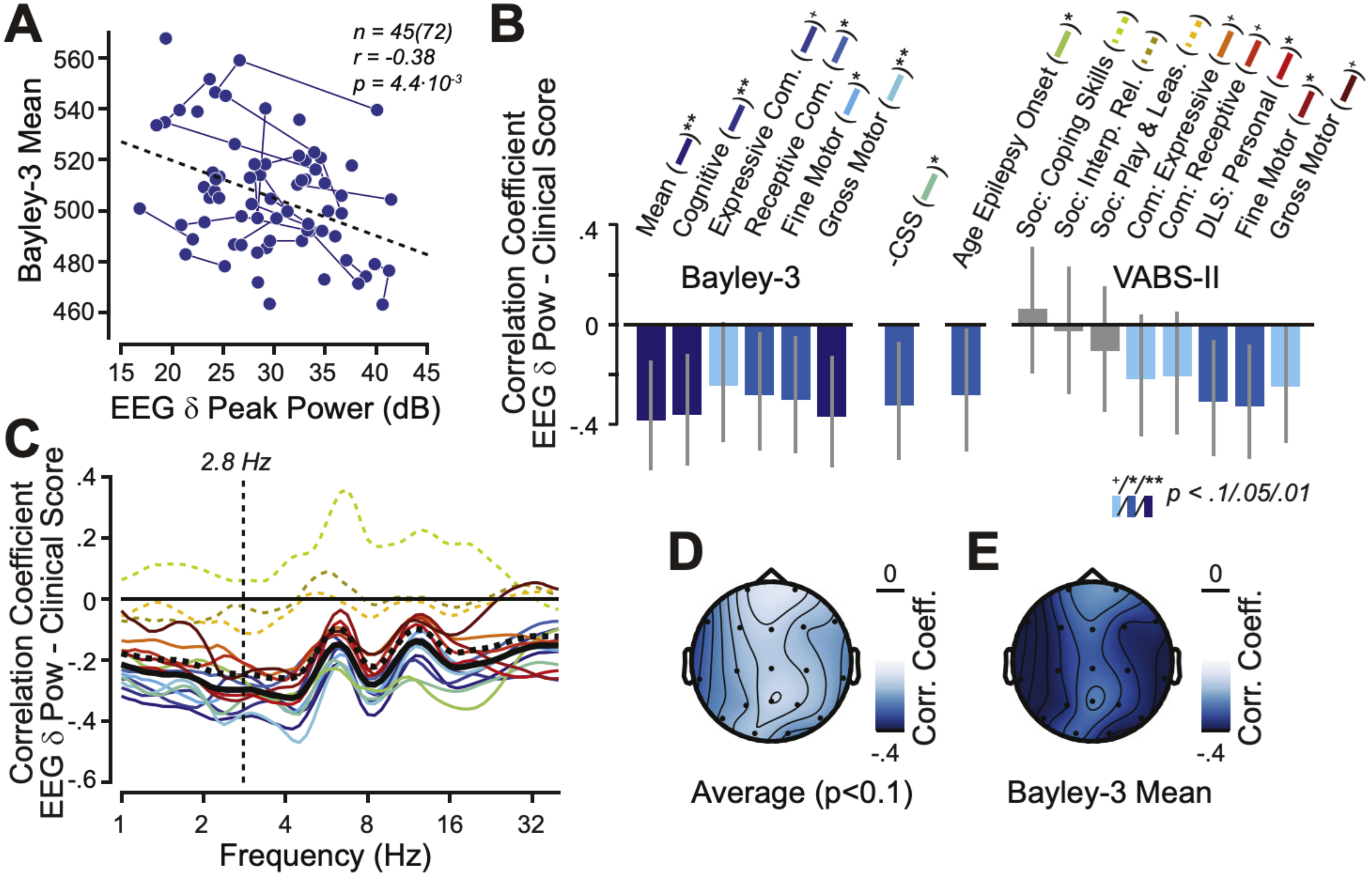
Table 3: Caregiver Impacts of SLC6A1-Related Disorder

Caregiver and Family Burden		Modifying Factors
Anxiety and stress	Injuries (risks higher due to assisting child with seizures, behavior, impulse control)	Access to therapy and adaptive equipment
Depression and guilt	Intimacy impacted	Coping strategies
Destruction of possessions and property by child	Medical and therapy appointments increased due to issues caused by child’s disorder	Support services, specifically child-care
Fatigue, exhaustion, disrupted sleep	Mobility reduced due to caregiving responsibilities	
Financial burden	Siblings and family interactions impacted	
Formal support system needed	Socialization and leisure activities reduced	
Household tasks difficult to complete	Work, reduced capacity	
Independence and agency decreased		

Caregiver experience linked to biomarker in patient?

EEG signature analyze with:

- Parental stress index
- Parental sleep
- Parental qualitative measure



Hipp et al, 2021

Canada's Drug and
Health Technology Agency

Boosting caregivers' role in measuring the value of new treatments in rare diseases

Laurie Lambert, PhD

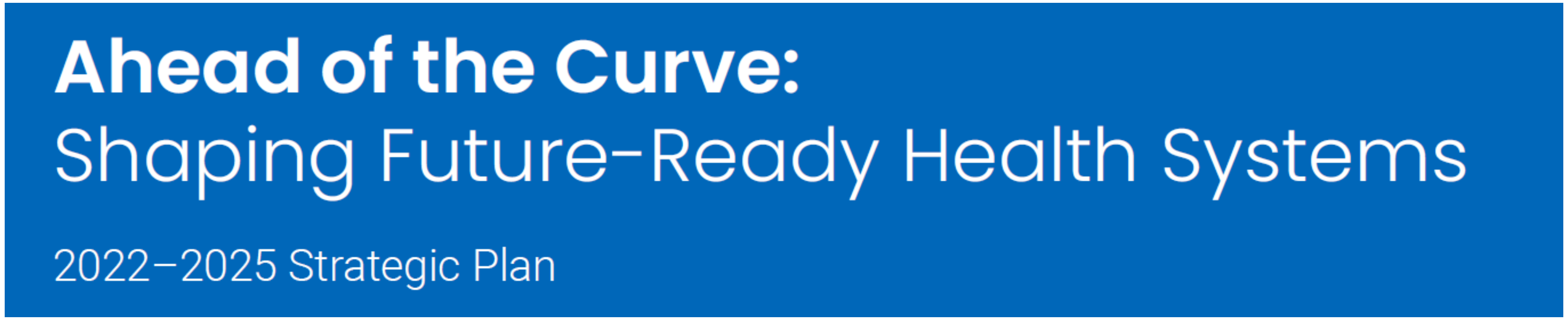
Lead, Real World Evidence, Evidence Standards

ISPOR Boston 2023

Context of this presentation

With the support of Health Canada, CADTH launched a **learning period** (2021/22 – 2022/23) during which the **potential value of real-world evidence (RWE)** to fill gaps in evidence and support decision making about **care for rare diseases** was explored through **collaborative learning-by-doing projects.**

CADTH has launched a new strategic plan:



Ahead of the Curve:
Shaping Future-Ready Health Systems

2022–2025 Strategic Plan

Some key messages from the literature about multistakeholder engagement

Participation in HTA processes by stakeholders such as the HTA workforce, patients, and clinicians is increasing (Trowman *et al*., 2020) and is **recognized as important** (Garrett *et al*., 2022)

Patient participation is particularly important for rare diseases, as **patients are experts in their pathologies** (de Andres-Nogales *et al*., 2021) and because of the degree of unmet need and limited clinical knowledge (HTAi, 2016)

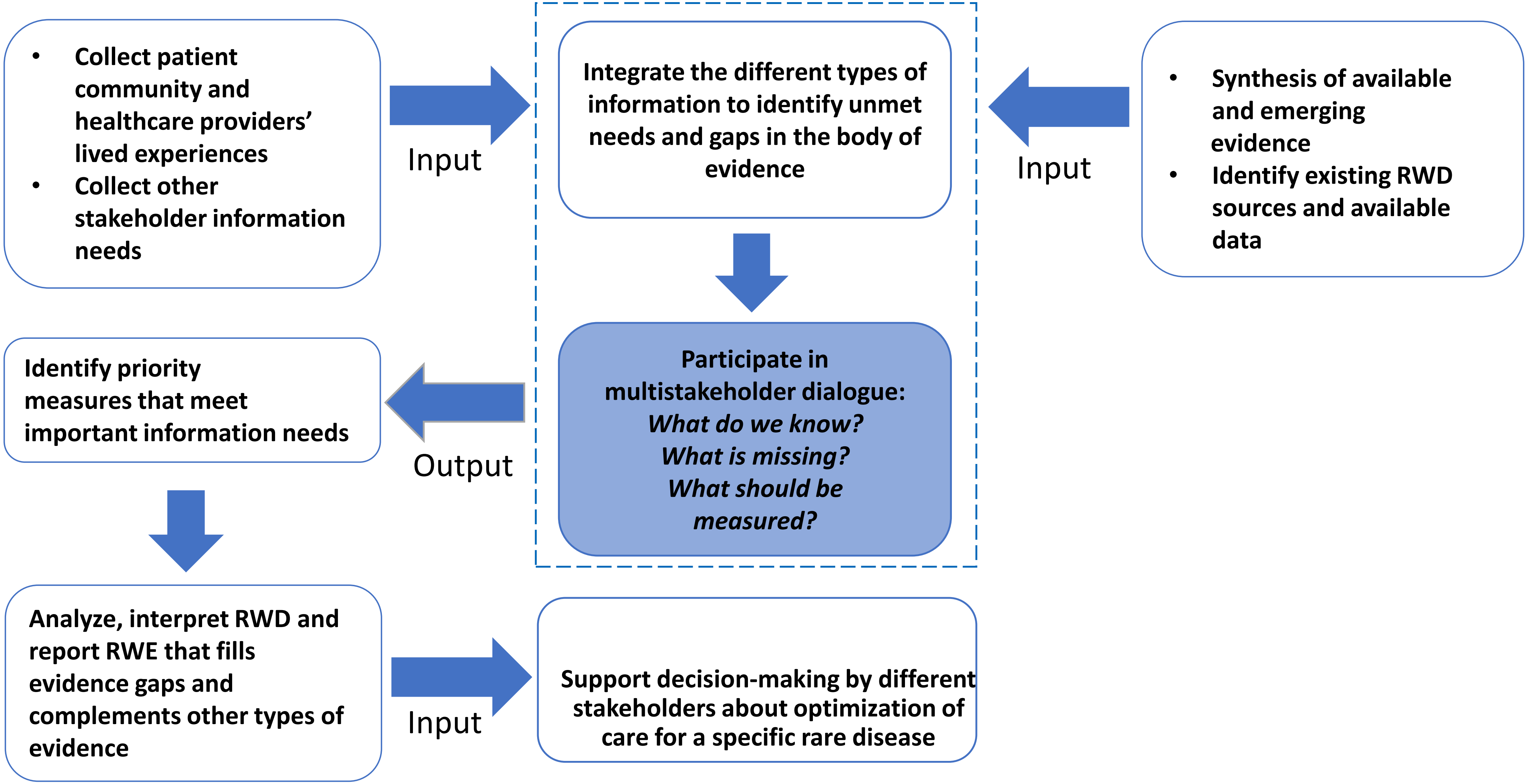
Involving **multiple stakeholders contributes to legitimacy of decision making** (de Andres-Nogales *et al*., 2021) and may increase stakeholders' acceptance of the decisions (Feenstra *et al*., 2022)

Multistakeholder involvement builds understanding among stakeholders, incorporates a range of values, and **supports quality decision-making** (Baltussen *et al*. 2021, Jiu *et al*. 2022, Oortwijn *et al*., 2021

Narrative Review of Multi-Stakeholder Engagement in Health Technology Assessment | CADTH

ISPOR Boston 2023

Exploring how to use different types of input to optimize decision-making



- Collect patient community and healthcare providers' lived experiences
- Collect other stakeholder information needs

Input

Integrate the different types of information to identify unmet needs and gaps in the body of evidence

Input

- Synthesis of available and emerging evidence
- Identify existing RWD sources and available data

Participate in multistakeholder dialogue:
What do we know?
What is missing?
What should be measured?

Output

Identify priority measures that meet important information needs

Analyze, interpret RWD and report RWE that fills evidence gaps and complements other types of evidence

Input

Support decision-making by different stakeholders about optimization of care for a specific rare disease

What do we know?

- Pediatric low-grade glioma is a rare disease with a Canadian incidence (2001-2015) for children 0-14 years of age of 1.41 cases per 100,000 person years
- Pediatric low-grade gliomas (pLGG) are the most frequent solid primary tumors of the central nervous system in pediatrics
- Median age of diagnosis: 6-8 y/o
- Canadian National Standard of Practice for CNS Tumors published in 2020
    - Standard practice treatments (chemotherapy and targeted treatments) for low-grade pediatric glioma are off-label with variation in route of administration (IV/oral)

Learning from listening to caregivers and patient groups

May 27th 2022 (6)*

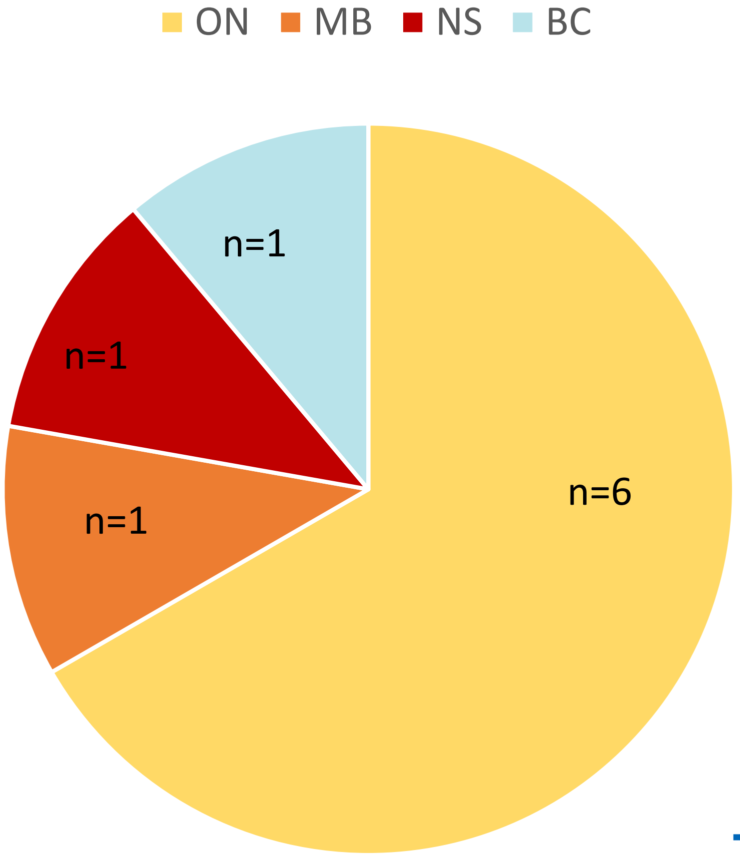
1 mother, 1 father, 3 patient group representatives

May 30th, 2022 (5)*

2 mothers, 1 father, 1 patient group representative

*1RN, Pediatric oncology as emotional support designate at each meeting

Regional Distribution of Patient Community Meeting Participants



What we learned from listening to caregivers and patient groups

Access to treatment:

- Accessing treatments is time-intensive for parents and their children and adds to the already heavy burden of caring for a sick child
- Reliance on communication with other families with lived experience, through virtual platforms, to guide them in their search for treatment options and what to expect from the care process
- At completion of clinical trials or treatment courses, families wait for the next steps in the care pathway

What we learned from listening to caregivers and patient groups

Financial burden of care:

- Drugs for pediatric oncology, and other rare diseases, can often be high-cost and issues can arise when they are prescribed “off-label”
- Out-of-pocket costs can also include:
    - medical tests and procedures,
    - medical supply and equipment costs for at-home care,
    - complementary alternative medicines (vitamins, supplements),
    - psychosocial support, childcare and other non-medical supports,
    - cost of travelling within or outside of Canada for their children to receive care (lodging, other accommodations, and/or transportation (gas, parking fees, public transit)
- Some have experienced misalignment in the language and requirements communicated between physicians and the insurance companies and this disconnect often falls on the family to manage

What we learned from listening to caregivers and patient groups

Other challenges:

- Orally administered versus intravenous therapies may be preferred because they can be administered outside of treatment centers
    - allows children to miss fewer days at school and with friends,
    - reduces burden on caregivers in terms of travel time,
    - reduces expenses and potential missed days at work
- Barriers associated with the transition from care in pediatric centers to adolescent/adult centers

Public drug reimbursement decision pathway in Canada

Health Canada asks:

Is it safe? Does it work?

CADTH asks:

How does it compare with existing treatment options? Is it good value

Federal, provincial, and territorial public drug plans and the pan-Canadian Pharmaceutical Alliance ask:

Is it needed? Is it affordable?

What decisions are being made by other stakeholders?

Industry: Where to invest (in which clinical trial?), what patient population, what to measure RCT/RWD?

Private payers: Should this treatment be reimbursed through private health insurance?

Healthcare providers: Should I offer this treatment or not and if so, when?

Caregivers: Should I give this treatment to my child? Will this treatment reduce my child's disease and care burden? Other side effects?

Patients: Should I take this treatment or not? Will this treatment reduce my disease and care burden? Other side effects?

Registry and data holders/researchers: What to measure and when?

Why did we have a multi-stakeholder meeting?

- **Purpose:** Today we want to hear your perspective and discuss as a group what type of information would be important for decision-making about optimization of care for pediatric low-grade glioma.

- **Objective:** More specifically, we would like to hear from each of you about what is most relevant to measure to meet your decision-making needs.

Pediatric Low-Grade Glioma Multi-stakeholder meeting

cadth Canada's Drug and Health Technology Agency

Pediatric Low-Grade Glioma Multi-Stakeholder Dialogue Methods and Practices

October 2022

[Pediatric Low-Grade Glioma Multi-Stakeholder Dialogue Methods and Practices (cadth.ca)]

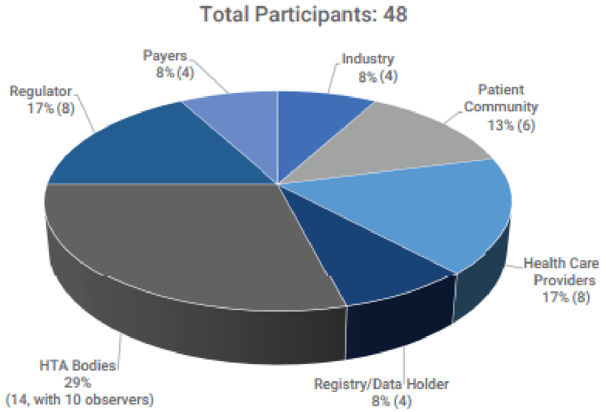
cadth Canada's Drug and Health Technology Agency

Multi-Stakeholder Dialogue: Optimizing the Use of Real-World Evidence for Decision-Making for Pediatric Low-Grade Glioma in Canada

What We Learned

[Multi-Stakeholder Dialogue: Optimizing the Integration of Real-World Evidence as Part of Decision-Making for Drugs for Rare Diseases (cadth.ca)]

Figure 1: Types of Stakeholders Present at the Multi-Stakeholder Meeting



What did you like most about the multistakeholder meeting?

"The level of engagement of clinicians, patients, and parent representatives was excellent!"

The indicators and outcomes identified in the discussions were grouped into 3 overarching categories: Patient Characteristics, Process of Care, and Outcomes.

Patient Characteristics	Process of Care	Outcomes
• Equity, diversity, and inclusion • Genetic conditions • Molecular tumour characteristics	• Treatment history • Nursing workload • Health care provider administrative burden • Prescribing data	• Financial burden for families and caregivers • Long-term outcomes • Patient-reported outcomes • Quality of life • Response to treatment

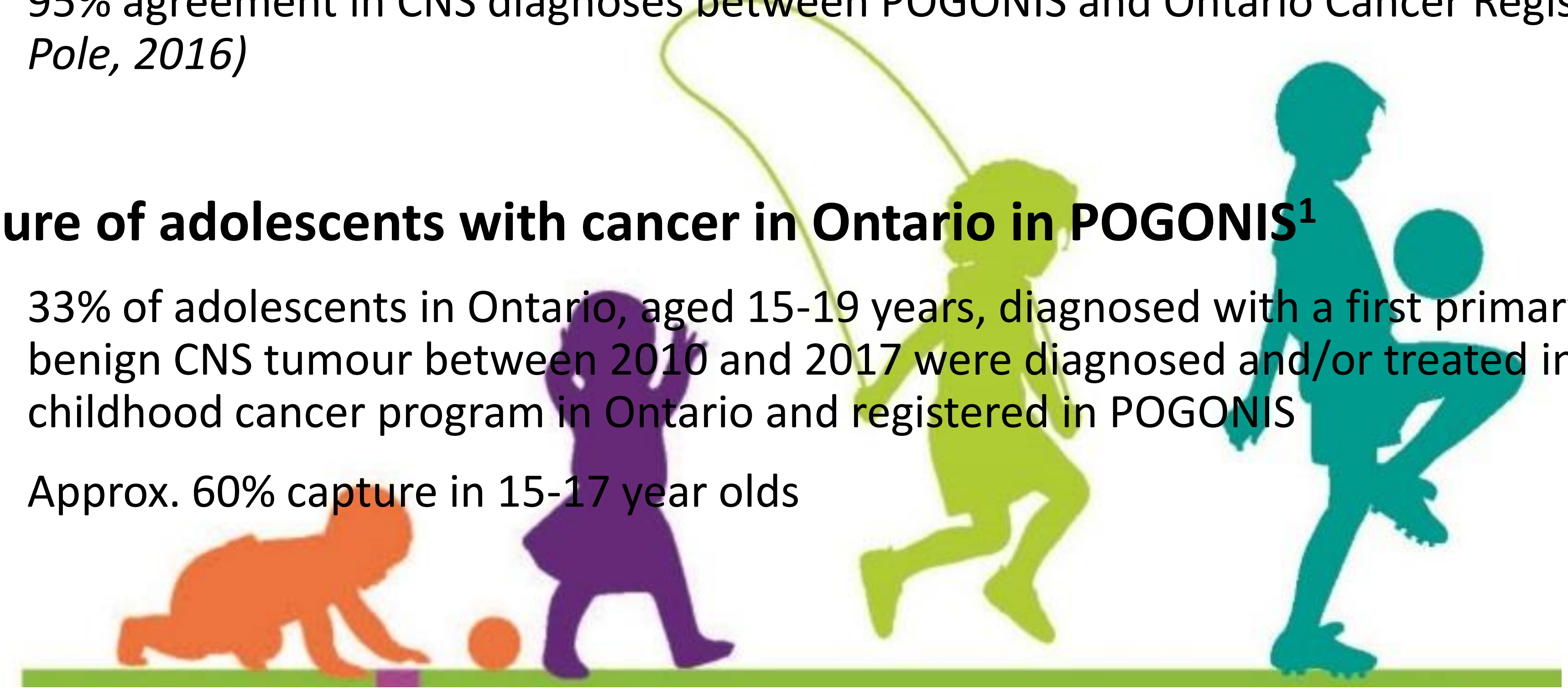
Explore potential sources of RWD

Complete population-based capture for 0-14 year olds diagnosed with cancer in Ontario

- 95% agreement in CNS diagnoses between POGONIS and Ontario Cancer Registry *(Gupta, Pole, 2016)*

Capture of adolescents with cancer in Ontario in POGONIS[1]

- 33% of adolescents in Ontario, aged 15-19 years, diagnosed with a first primary cancer or benign CNS tumour between 2010 and 2017 were diagnosed and/or treated in a specialized childhood cancer program in Ontario and registered in POGONIS
- Approx. 60% capture in 15-17 year olds



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[1] *<u>Data Source</u>: Ontario Health and Pediatric Oncology Group of Ontario. Adolescent and Young Adults (AYA) Cancer Cohort, 2020.*

Next Steps

Partnership

We will cultivate meaningful relationships with patient communities (including individual patients, their families and caregivers, and those who represent patients); clinicians; industry; other health organizations; and federal, provincial, and territorial governments; informing, engaging, and respecting our partners to together improve and strengthen the quality and significance of our work.

Innovate and collaborate on the use of real-world evidence (RWE). To unlock the potential of new products where the evidence is still evolving through understanding the impact in the real world, including drawing on patient-level experiences, we will identify new ways of bridging the evidence gaps. CADTH will actively shape the pan-Canadian discussion on how best to generate, gather, and optimize the use of RWE, drawing on our methods, knowledge, experience, and expertise, including from a wide range of domestic and international partners.

Ahead of the Curve:
Shaping Future-Ready Health Systems

2022–2025 Strategic Plan

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Thank you

Q&A

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