Panel Discussion 5: Considerations for the Implementation of Clinical Outcome Assessments in Pediatric Drug Development Programs

FOURTH ANNUAL
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

April 25, 2013 ■ Silver Spring, MD

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Session Outline

- Introduction
- Presentations
  - Pediatric Regulations 2012: Permanent Laws and New Provisions under FDASIA
  - Pediatric PROs for Intellectual Disability: Learning from Down Syndrome
  - Outcome Measures for Clinical Trials: Individuals with Intellectual and Developmental Disabilities (IDD)
- Discussion Panel
- Q & A

Session Participants

- **Moderator**:
  - *Melissa S. Tassinari, PhD, DABT* – Senior Clinical Analyst, Pediatric and Maternal Health Staff, OND, CDER, FDA
- **Presenters and Panelists**:
  - *Melissa S. Tassinari*
  - *Omar Khwaja, MD, PhD* – Translational Medicine Leader, Neurosciences, F.Hoffmann-LaRoche AG
  - *Tiina Urv, PhD* – Health Scientist Administrator, Intellectual and Developmental Disabilities Branch, National Institute of Child Health & Human Development
- **Additional Panelists**:
  - *Nicholas Kozauer, MD* – Acting Clinical Team Leader, Division of Neurology Products (DNP), CDER, FDA
  - *Ranjit Mani, MD* – Medical Reviewer, DNP, CDER, FDA
  - *Elektra Papadopoulos, MD, MPH* – Endpoint Reviewer, SEALD, OND, CDER, FDA
  - *Juliana Setyawan, PharmD, MS* – Director in Global Health Economics and Outcomes Research/Epidemiology, Shire Development, LLC
  - *Diana Rofail, PhD, CPsychol* – Global Head of Patient-Reported Outcomes, CNS & Metabolism, Product Development, Biometrics, EpiPRO, Roche Products Ltd

Pediatric Regulations 2012: Permanent Laws and New Provisions under FDASIA

Melissa S. Tassinari, PhD DABT
Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
April 25, 2013

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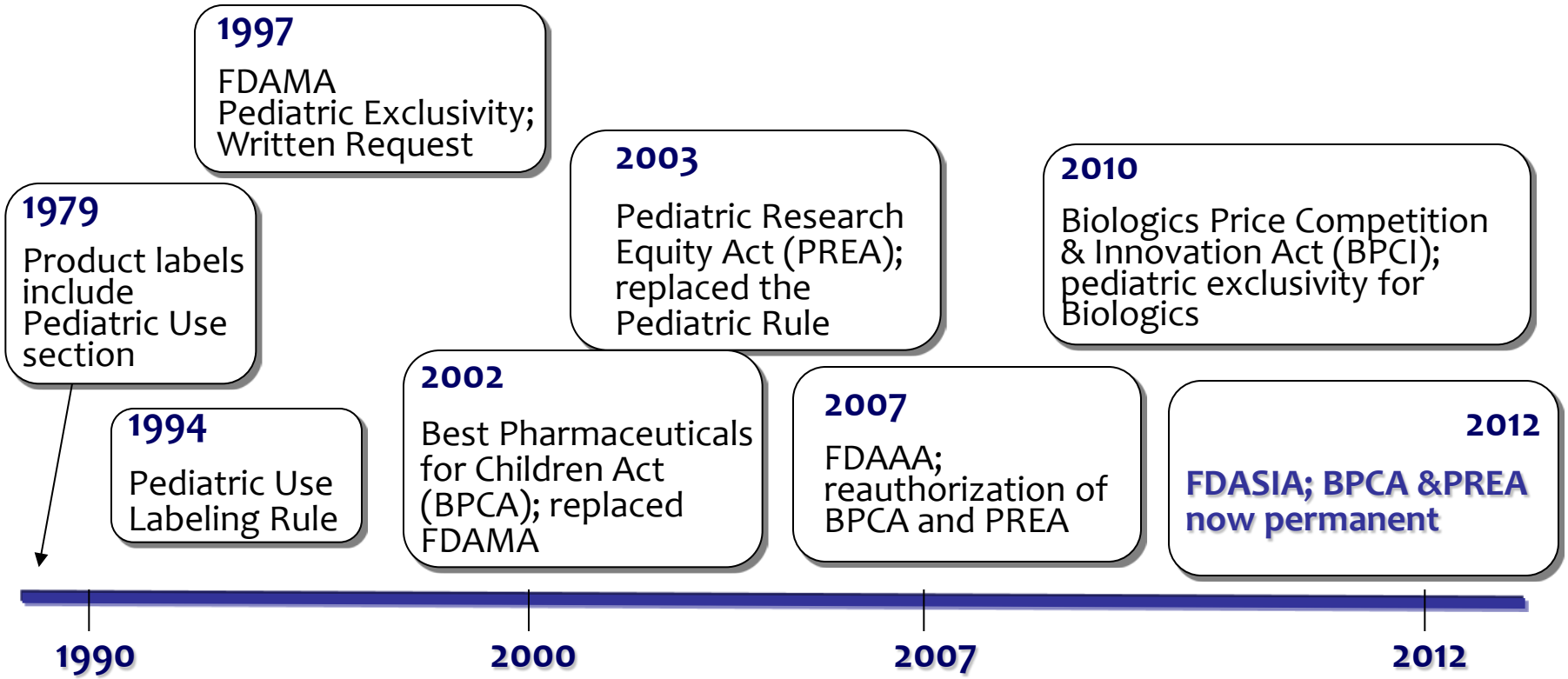
Pediatric Regulatory History



Acronyms

- BPCA – Best Pharmaceuticals for Children Act
- FDAAA – Food and Drug Administration Amendments Act
- FDASIA – Food and Drug Administration Safety and Innovations Act
- PAC – Pediatric Advisory Committee
- PeRC – Pediatric Review Committee
- PPSR – Proposed Pediatric Study Request
- PREA – Pediatric Research Equity Act
- PSP – Pediatric Study Plan
- WR – Written Request

US Pediatric Laws: PREA and BPCA

John Singer Sargent

PREA

Studies mandatory

Required studies for adult indication under review

Applies to drugs and biologics

Not required for orphan indications

BPCA

Studies voluntary

Studies for entire active moiety (all relevant indications)

Applies to drugs and biologics

WR may be issued for orphan indications

BPCA: Written Request (WR)

- A description of pediatric studies
  - issued by a Review Division
  - Can be in response to a PPSR
  - Can be for indications and conditions other than the adult indication
- Considerations
  - What is the public health benefit?
  - Are the study designs feasible; sufficient to support dosing, safety and efficacy?
  - Have all populations and conditions been addressed?
  - Are there other products already approved for the condition?
- Successful completion results in an award of 6 months exclusivity attached to the patent

FDASIA 2012

- New requirements for Pediatric Study Plans
- Provision for extension for deferred studies
- Neonates and the Written Request
- Pediatric Priority Review Voucher

Changes under FDASIA

- Pediatric Study Plans - PSPs
  - Sponsors required to submit plans at End of Phase 2
- Must include:
  - Outline of the pediatric study or studies that the applicant plans to conduct *(including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach)*
    - Template available on line *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm*
  - Any request for a deferral, partial waiver or waiver, along with supporting information
- Draft guidance should be available in 3 -4 months

Developing the Pediatric Study Plan

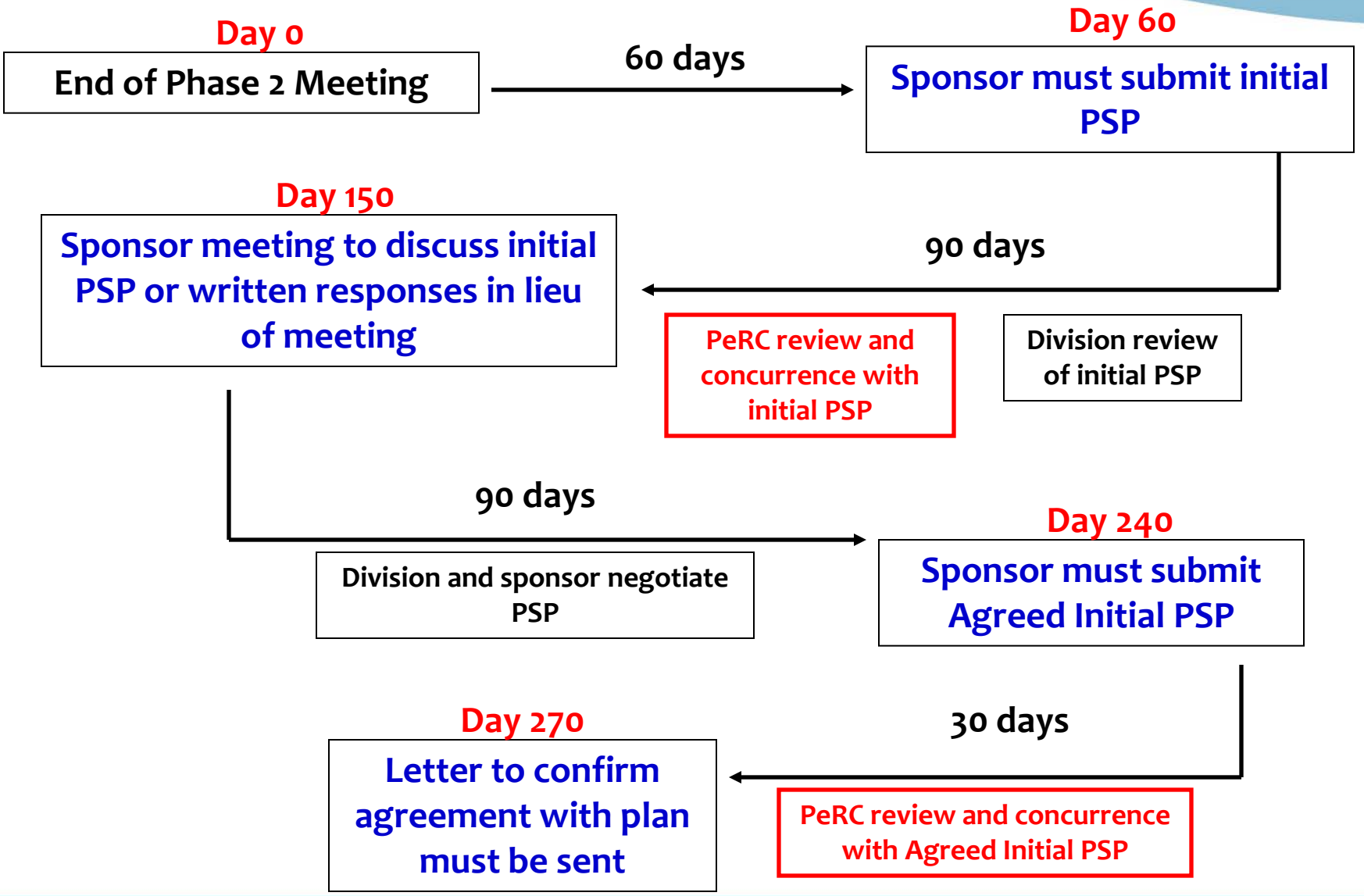
- Overview of the disease in the pediatric population for the product under development
- Potential plans and justification for use of extrapolation
- Plans and justification for full or partial waiver
- Plans for pediatric specific formulation development
- Nonclinical data, complete or planned, to support studies in children
- Synopsis/summary of all clinical studies planned
- Timeline for the Pediatric Study Plan
- Provide any agreements with other Health Authorities (e.g., PIP for EMA)

Pediatric Investigation Plan [PIP]; European Medicines Agency [EMA]

Timing of PSP Submission

- EOP2 meeting occurred on or after November 6, 2012
  - PSP must be submitted within 60 days of the EOP2 meeting
- EOP2 meeting occurred prior to November 6, 2012 or no EOP2 meeting will occur
  - If application expected to be submitted prior to January 5, 2014, FDAAA rules apply and pediatric plan must be submitted no later than the application is filed
  - If application will be submitted on or after January 5, 2014, PSP should be submitted as early as possible and at a time agreed upon by FDA and sponsor.
- FDA strongly encourages PSP to be submitted prior to the initiation of Phase 3 studies.
- PSP must be submitted no later than 210 days prior to submission of application.

Timeline for Pediatric Study Plan Review



PREA Under FDASIA

- New provision to allow extension for deferred studies under PREA
- General criteria for acceptance of extension requests
  - Provide general consistency with reasons for delayed FDAAA Post Marketing Requirements [PMRs]
  - Delay in development could not have been prevented or could not have been foreseen
  - Sponsor will still be able to complete the studies

FDASIA and the Written Request

- No changes in the process
  - PPSR submitted by sponsor or WR generated by FDA
- Inclusion of neonates (birth – 28 days)
  - All age groups must be considered and included where appropriate
  - If inclusion of neonates is not warranted a justification must appear in the WR
    - Disease does not occur in this age group
    - Studies are not feasible or safe

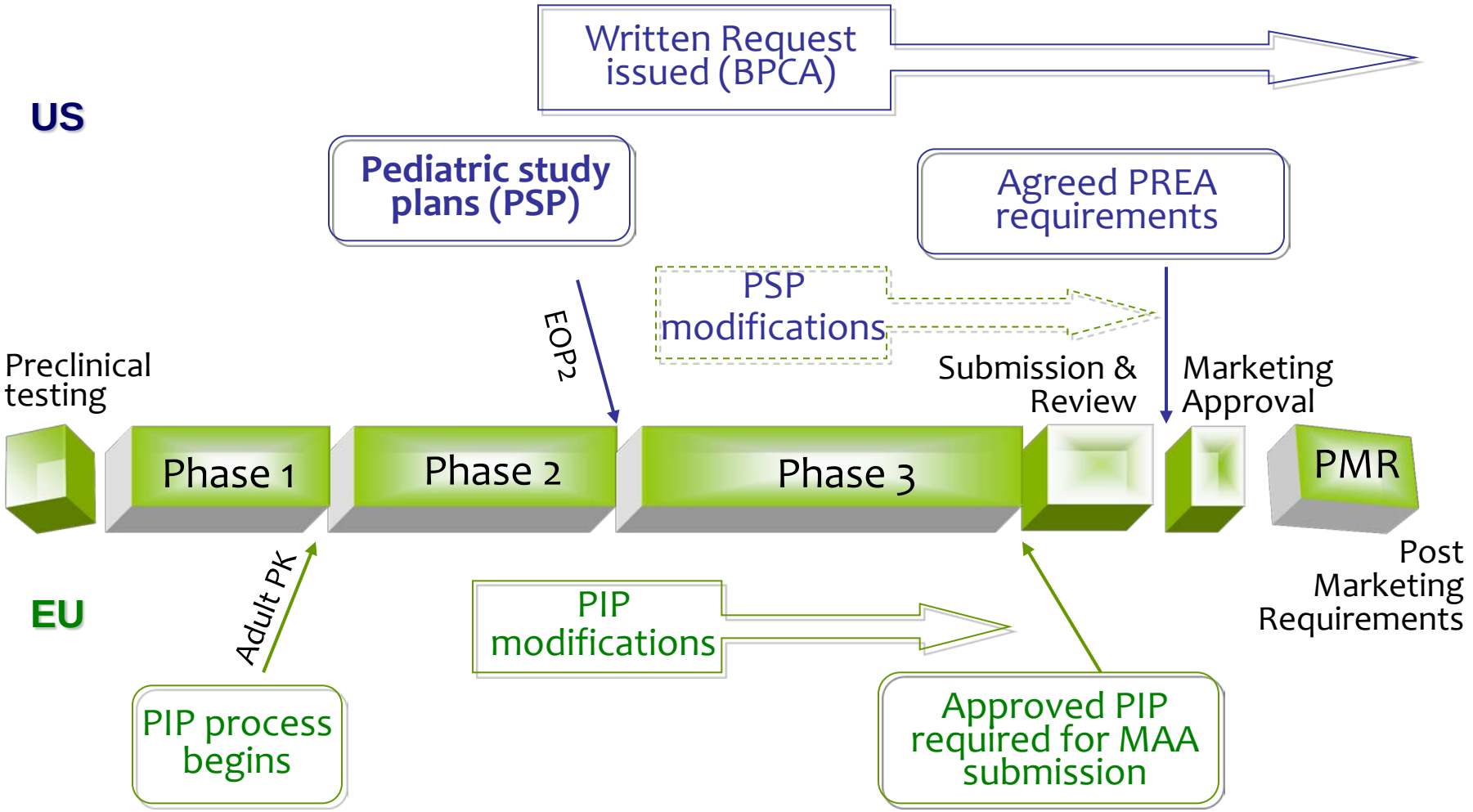
FDASIA - Pediatric Priority Review Voucher

- For development of products for rare pediatric disease
- Provides a voucher for 'priority review' of any subsequent human drug application.

FDASIA - Pediatric Priority Review Voucher

- Definition of a rare pediatric disease
  - "disease that primarily affects individuals aged from birth to 18 years, including age groups often called neonates infants, children and adolescents"
  - meets the definition of 'rare disease or condition' as set forth in the Orphan Drug Act
- 3 pronged requirement
  - Meet definition above
  - Provide clinical data from studies in the intended pediatric population – including dosing information
  - Are not seeking approval for an adult indication in the original rare pediatric disease product application

Pediatric Planning in the Drug Development Process



Marketing Application Authorization [MAA]


T H E E N D

Pediatric PROs for Intellectual Disability: Learning from Down Syndrome

Omar Khwaja MD PhD and Diana Rofail PhD
Neurosciences, F. Hoffmann-La Roche AG

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Intellectual disability

Intellectual disability is a disability characterized by significant limitations both in:

intellectual functioning
and
adaptive behavior.

This disability originates before the age of 18.

aaidd
American Association on Intellectual and Developmental Disabilities

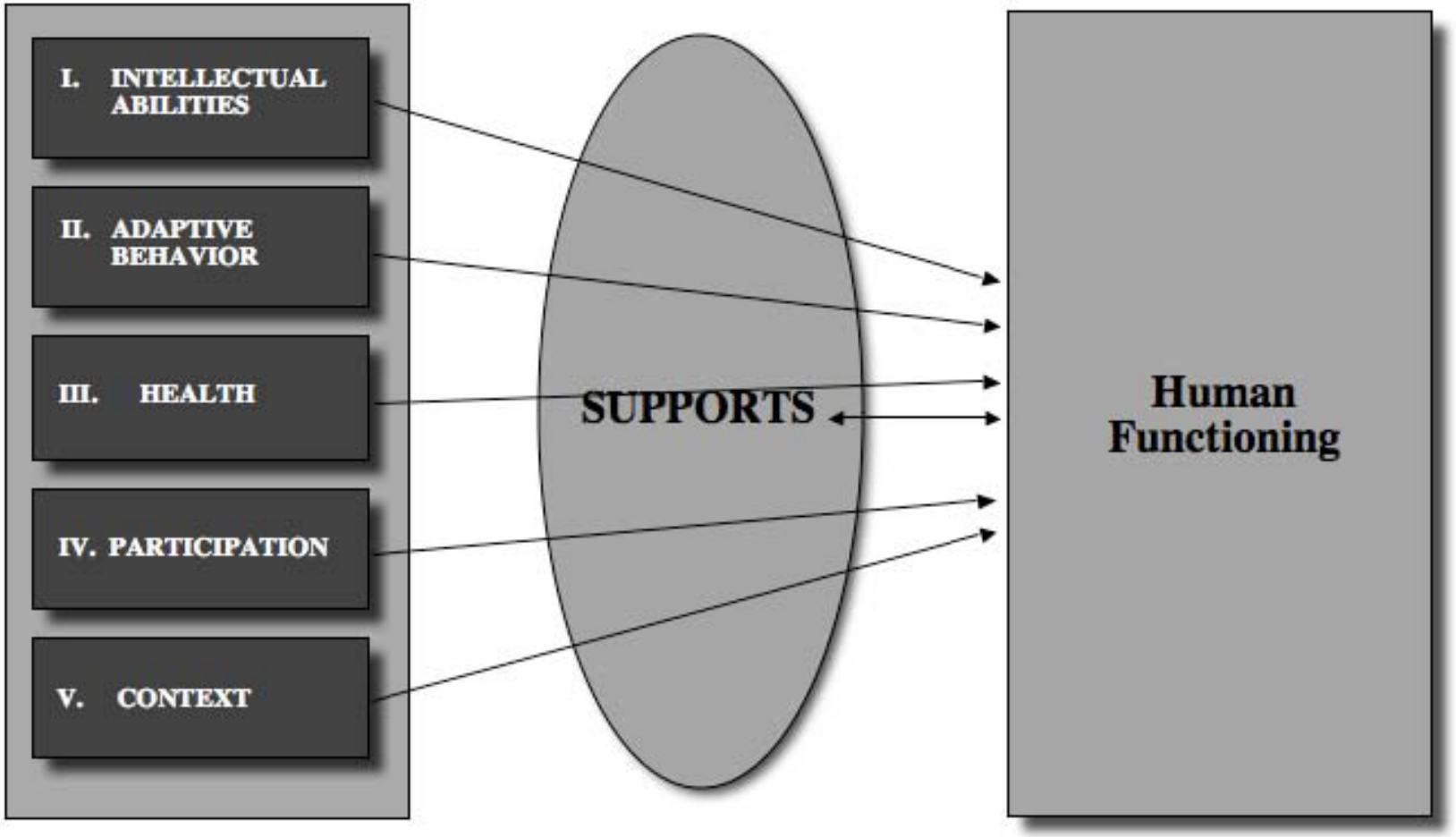
World Health Organization
Europe

European Commission

5 assumptions about ID in PRO development

- Limitations in present functioning must be considered within the **context** of community environments typical of the individual's age peers and culture
- Valid assessment considers cultural and linguistic **diversity** as well as differences in communication, sensory, motor, and behavioral factors
- Within an individual, limitations often coexist with **strengths**
- An important purpose of describing limitations is to develop a profile of needed **supports**
- With appropriate personalized supports over a sustained period, the life functioning of the person with intellectual disability generally will **improve**

Conceptual framework of human functioning



Intellectual and Developmental Disabilities

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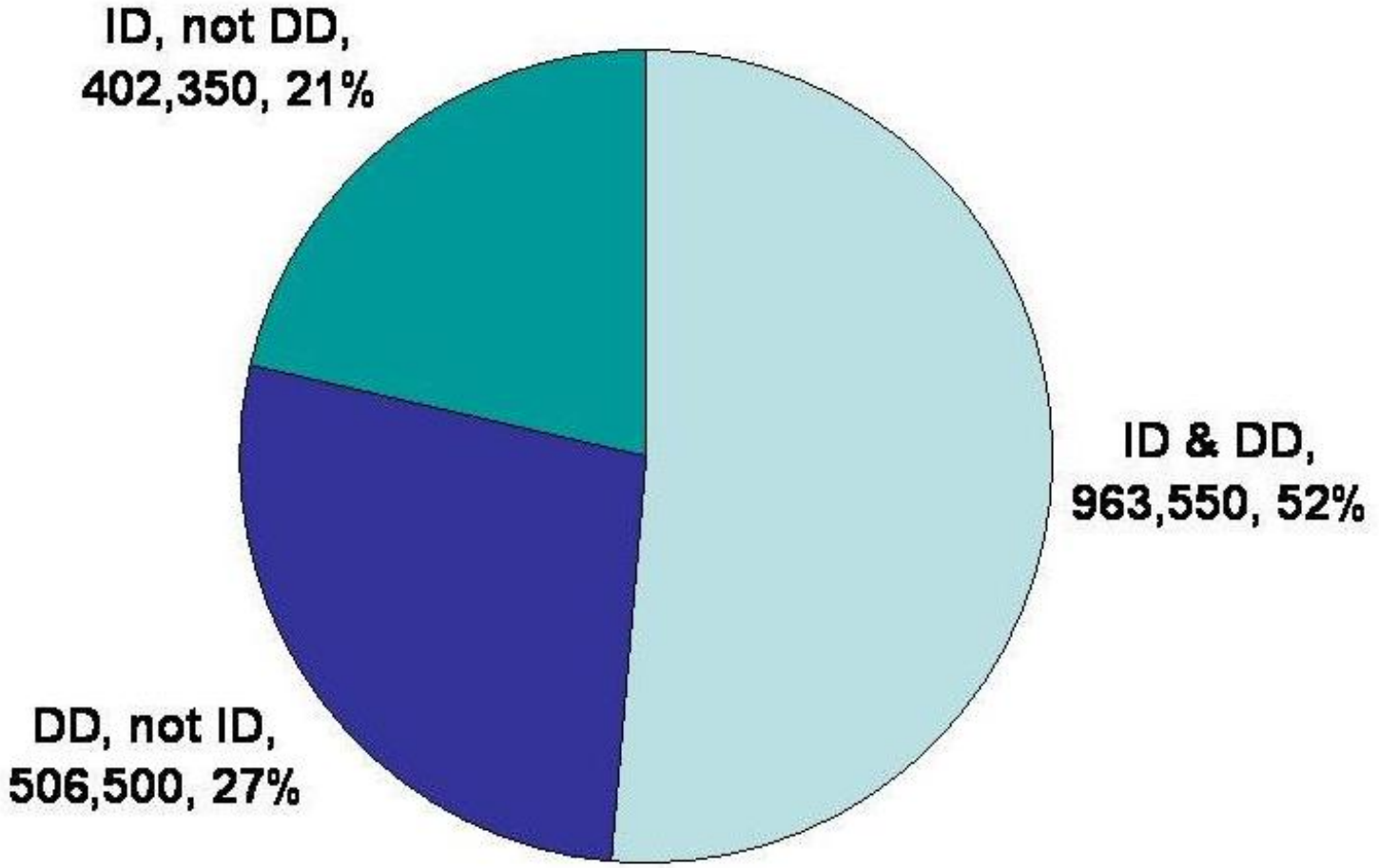
- ID of all causes
  - Known causes
    - Genetic causes
      - Down syndrome
      - Fragile X syndrome
      - Rett syndrome
      - Other genetic causes
    - Non-genetic causes
      - Fetal alcohol syndrome
      - Other teratogenic causes
      - Infections
        - Meningitis
        - Other
      - Other adverse events such as head injury
  - Unknown causes

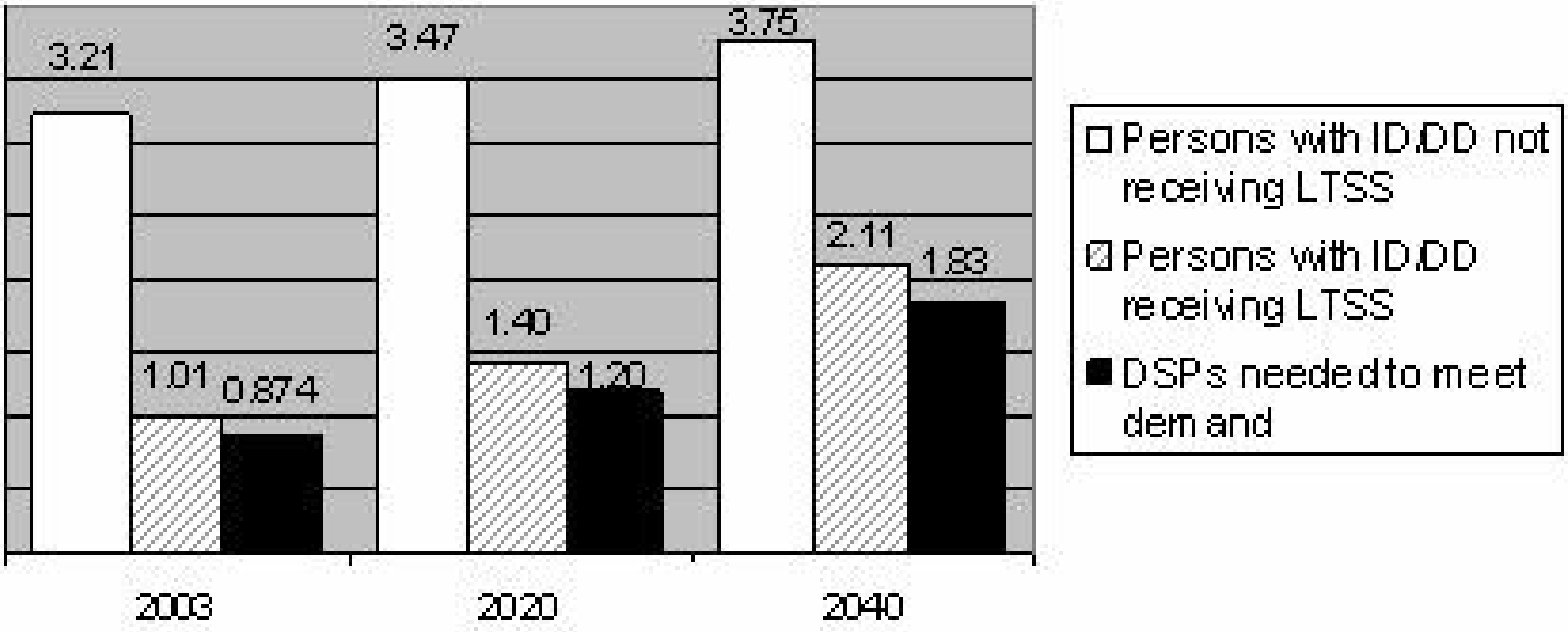
Adults (18+) with ID ± DD



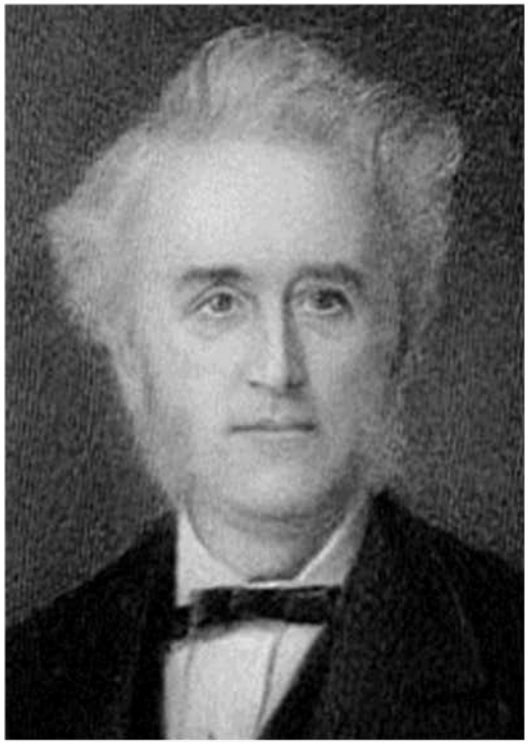
DHSS 2006

Rising demand

Figure 5. Estimated Prevalence of Intellectual and Developmental Disabilities, Long-Term Service and Support Demand and Needed Direct Support Professionals in 2003, 2020 and 2040 (in millions)



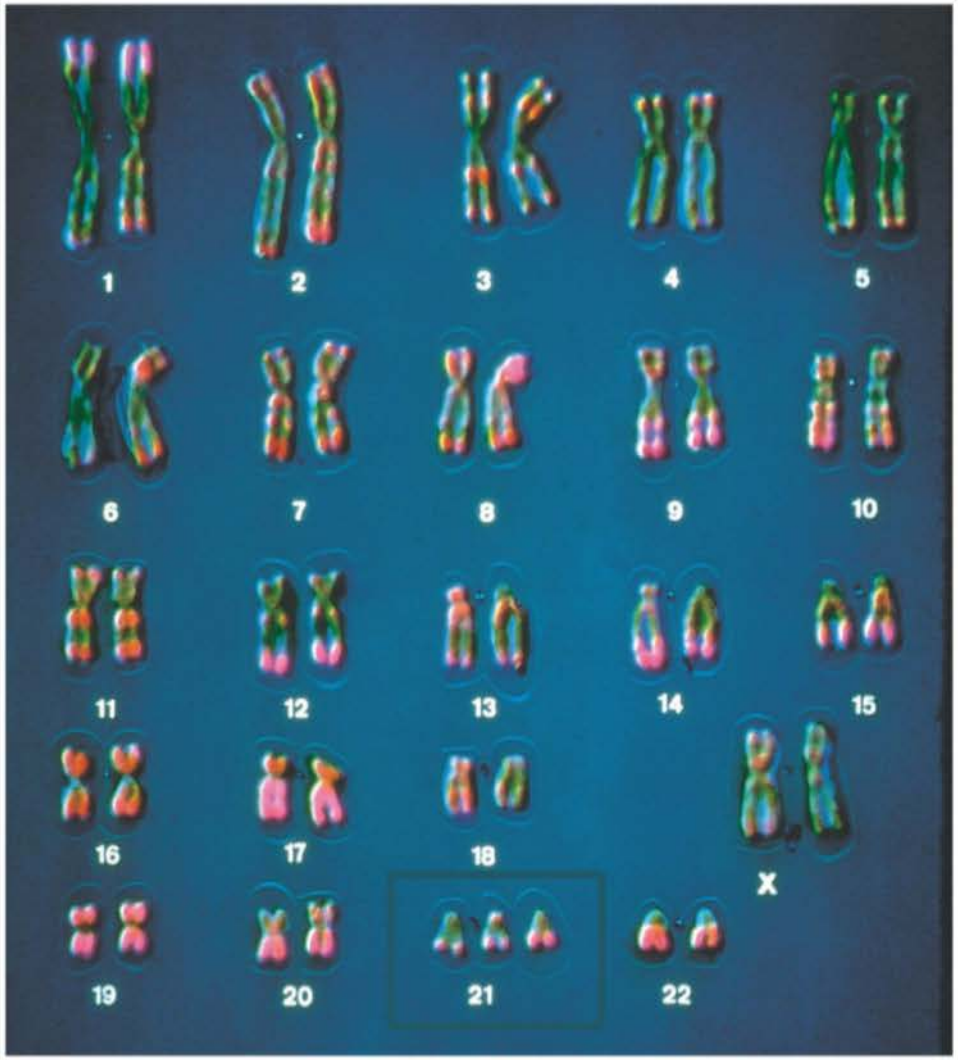
Down syndrome



John Langdon Down
1866

Jaguar Children
Olmec 1400-400 BC

Down syndrome and T21



Jerome Lejeune
1958

Down Syndrome

Affects over 30,000 newborns in 8 major regions per year

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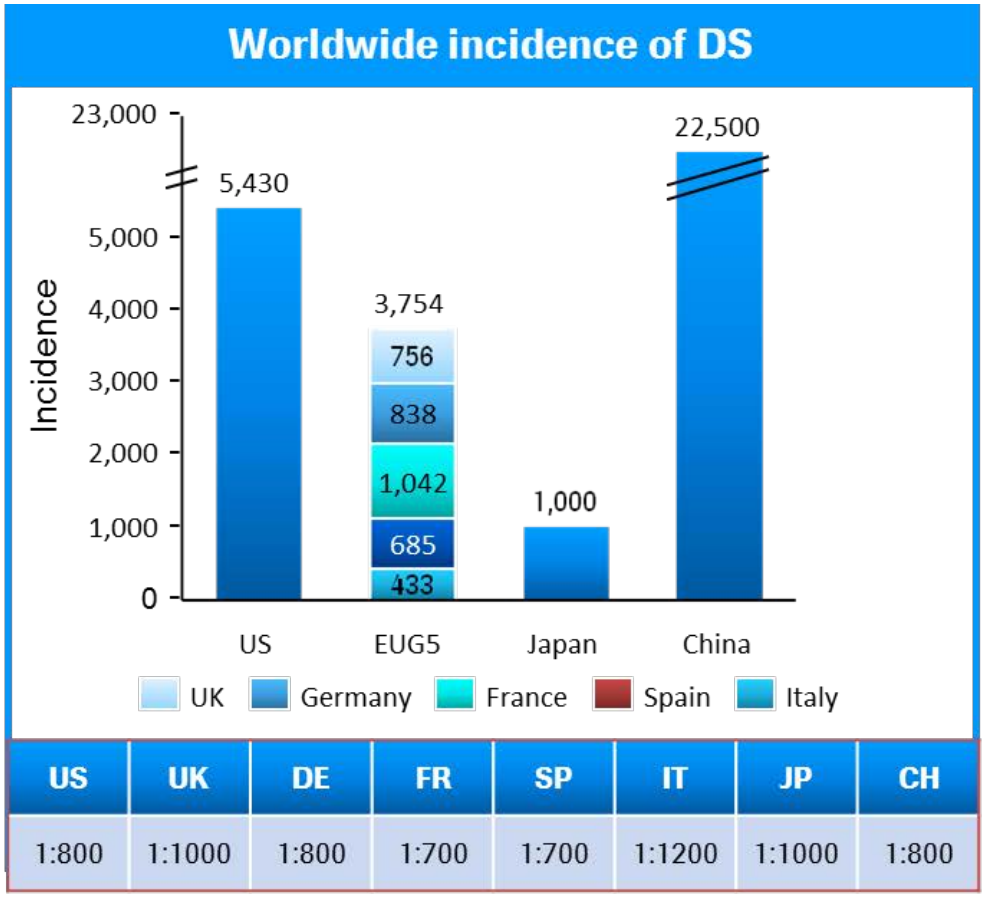
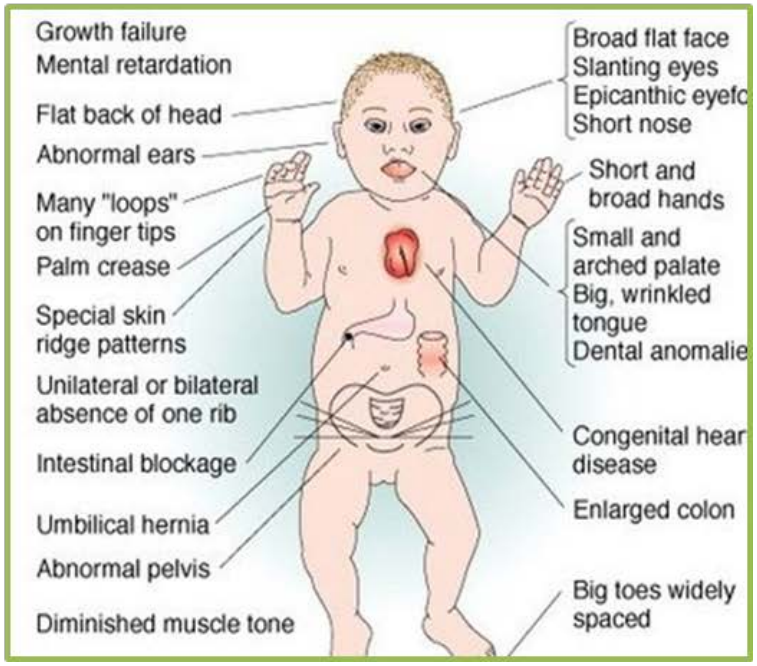
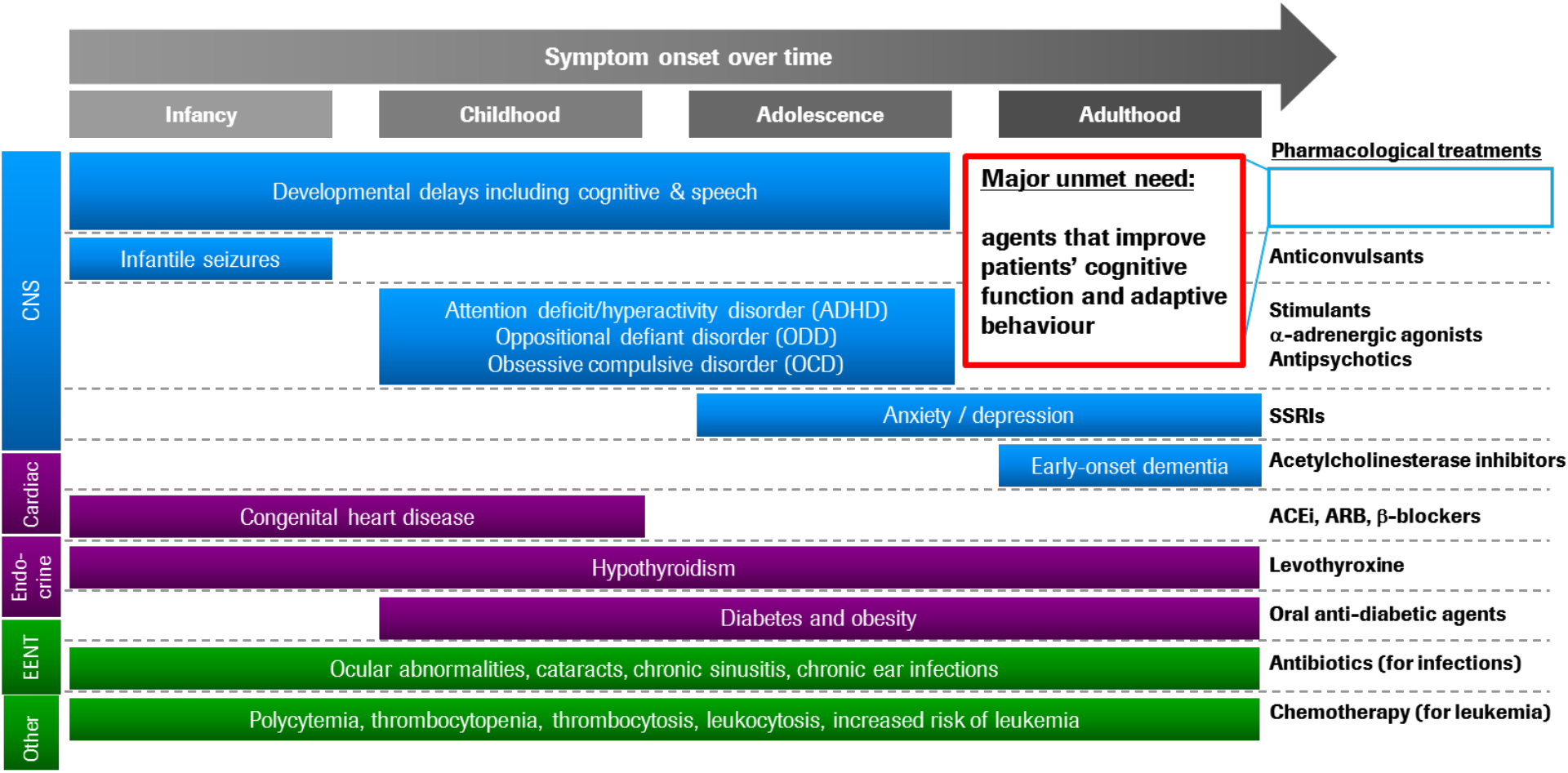


US	UK	DE	FR	SP	IT	JP	CH
1:800	1:1000	1:800	1:700	1:700	1:1200	1:1000	1:800

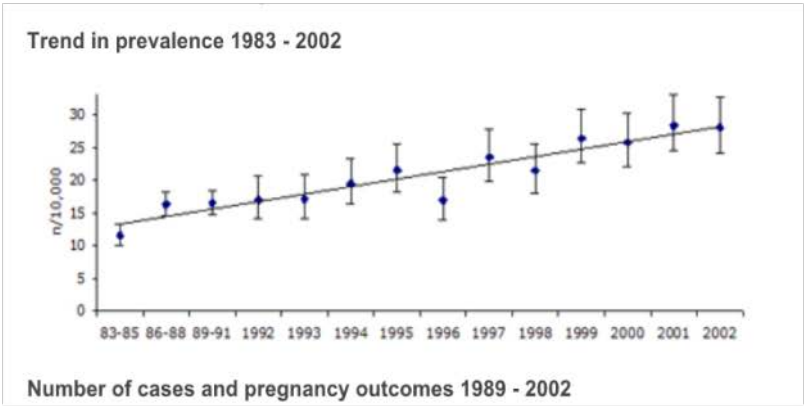
Methodology: UNDP birth cohort data has been used to calculate total DS incidence per country

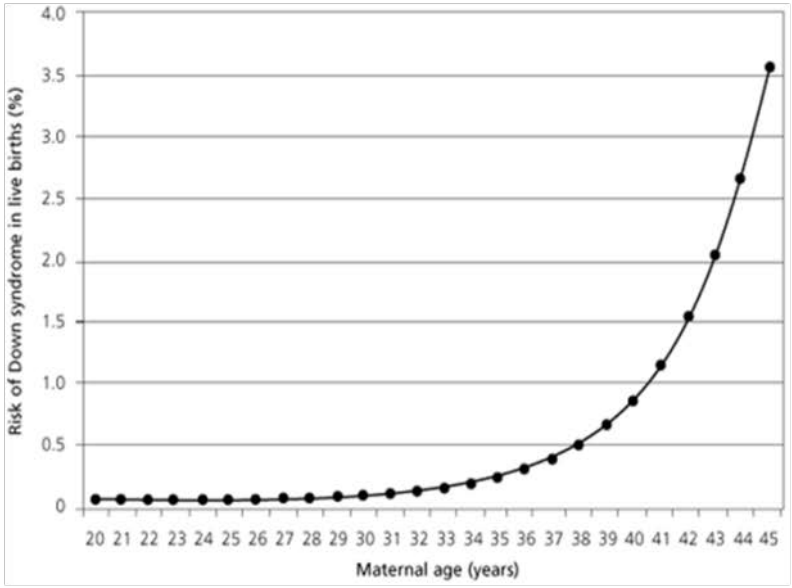


Down syndrome through the lifespan



Stable or rising incidence





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Parents / Caregivers

Education

- **Poor concentration** on lessons
- Does not want to **attend**
- No interest in children **of own age**
- **Teased/bullied** by other children
- **Over-friendly** with other children (i.e. Kissing)
- **Toilet accidents**

Examples of day to day challenges of young people with DS

Leisure

- Prefers to **stay at home**
- Unable to take part in **team games** due to coordination difficulties
- Does not remember to **pack own kit** for sports/activities
- Unable to keep spending on luxuries to a **budget**

Travel

- Forgets routes and gets **lost**
- Cannot catch right **bus or train** without help
- May not **dress appropriately** for the weather
- Hard to **communicate with others** and be understood for help or directions

Stigma

When we go out in public, they look at her like she has a disease. I want to turn around and shout that they can't catch anything!

Parent, US

At Home

- Cannot apply **sanitary towels** properly
- Irregular **sleep patterns** lead to daily tiredness
- Requires help to maintain **cleanliness**
- Unable to prepare **own meals**

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Things Parents / Caregivers wish that the person they care for…

Parents / Caregivers

Could do

- Speech
- Adapt
- Education
- Behaviour
- Socialize
- Concentrate
- Sleeping
- Work

She lacks the confidence to go somewhere new by herself. If it isn't a regular journey, I have to accompany her.
Parent of patient age 18-23, US

Even though he's tired, he would rather hit the bed frame with his head than go to sleep. That disturbs our life very much.
Parent of patient age 6-11, China

He will lose concentration and go into his own world and talk to himself, and we have to snap him out of it. He will do this about once a day.
Parent of patient 6-11, US

Since he is unable to work, providing for him is a financial consideration. He is unable to contribute.
Parent of patient age 6-11, China

Speaking, expressing herself better. You know she has a lot in her head that she wants to express but she can't really get it out.
Parent of patient age 31+, Germany

I would like him to be able to read and write better, this is important in order to fit into society better.
Parent of patient age 24-30, France

She won't initiate play with others because there is a fear of being made fun of.
Parent of patient age 31+, US

He does not go to sleep until very late and high energy after school. We believe he may have a sleep disorder.
Parent of patient age 6-11, US

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Things Parents / Caregivers wish that the person they care for…

Parents / Caregivers

Could do independently

- Hygiene
- Socialise
- Dress self
- Homework
- Be at home
- Eat / Chew

He always makes a mess when he tries to wash himself, and doesn't know what to get out to prepare.
Parent of patient 12-17, US

Sometimes I worry that he won't meet anybody when I am gone in the future. What will happen when I am gone?
Parent of patient age 31+, France

Being able to dress himself alone correctly would give my son much more independence, and he would be so proud of himself.
Parent of patient age 6-11, France

Learning is difficult because his memory is so poor, mostly in terms of word specific learning, as well as logic and mathematics.
Parent of patient age 18-23, China

I always need someone in the house (with her), so even if I want to go to the shops then I need someone around.
Parent of patient age 18-23, US

If he were able to eat by himself it would make things easier and much more comfortable for him, and it would also give him a sense of success.
Parent of patient age18-23, Germany

Parent and carer comments

"I fear her being made fun of, not at the start because she won't stand out but once they get to know her, her immaturity will stand out." **Caregiver, USA**

"Sometimes I worry that he won't meet anybody when I am not around in the future. I worry what will happen when I am gone." **Caregiver, France**

"It would be good if my son was able to dress himself, that would give him more independence ." **Caregiver, France**

"It is difficult to understand him when he talks , it requires experience. I will often have to ask him to repeat himself." **Caregiver, Germany**

Translational research in Down syndrome

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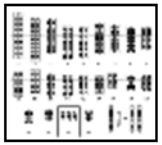
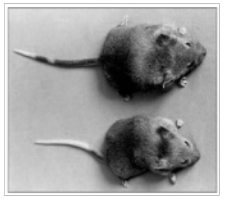
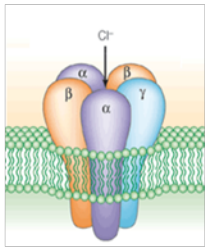
Down syndrome



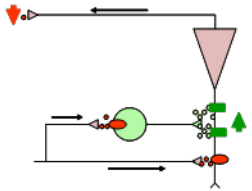
Cognition
Impaired learning and memory
Hippocampal dysfunction

Ts65Dn mouse model

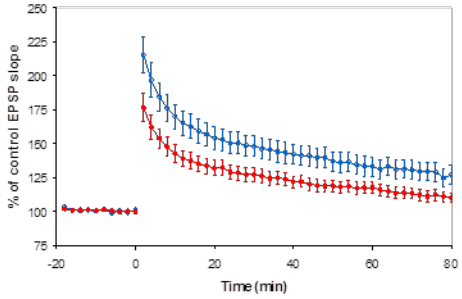




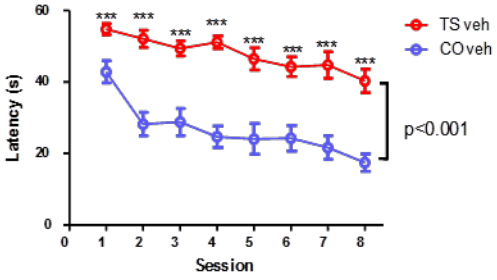
$GABA_A$ Receptor



Circuitry



Physiology



Behaviour

Development requires a new approach

2010		2011				2012				2013				2014			
Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4

PH 1 HV SAD/PET and MAD

PH1 Multiple Dose in adult DS – BP25543

Non-Drug observational - BP25612

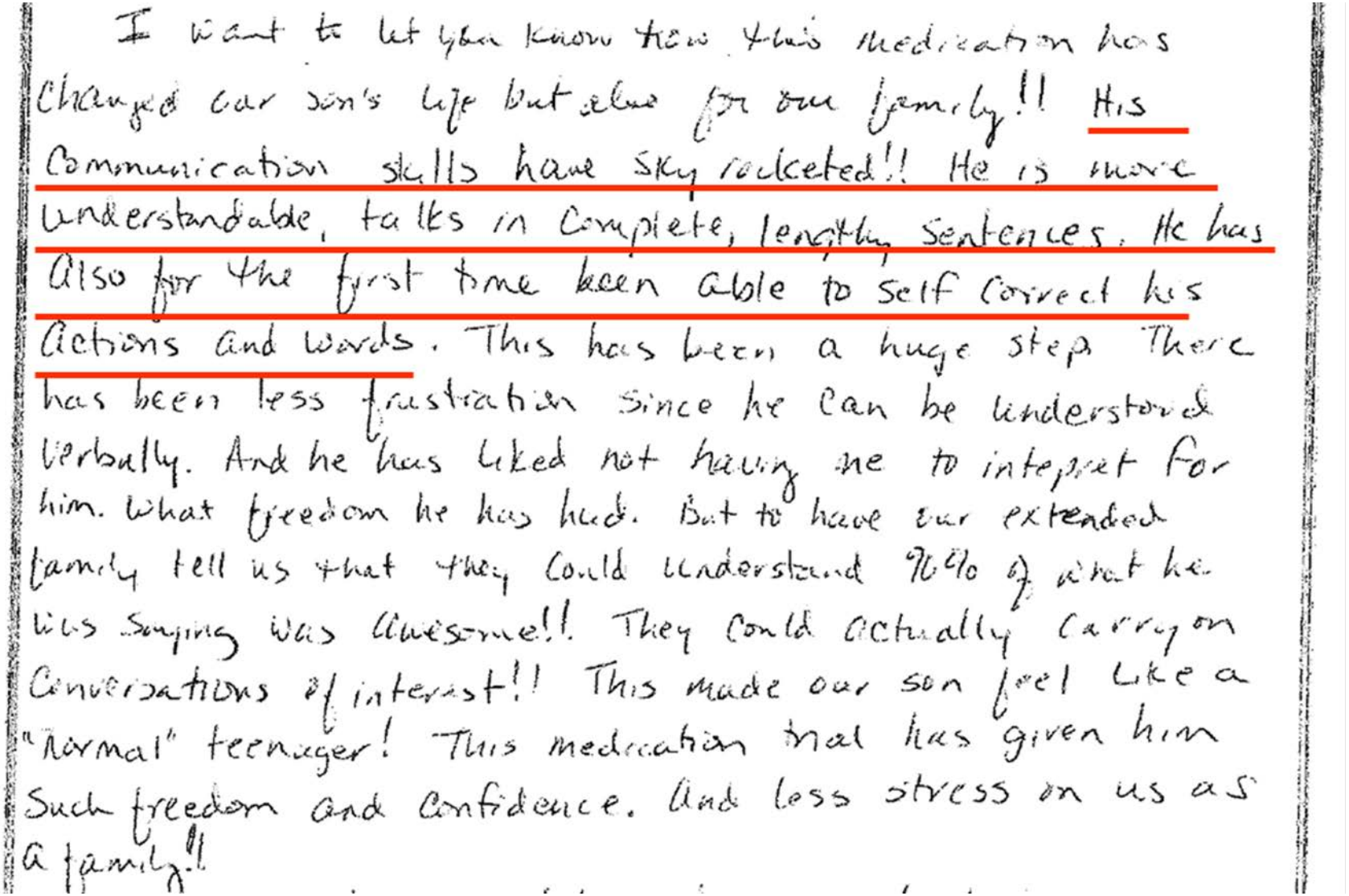
PET study Adult DS - BP25611

Ph2b LIP enabling Study Age 12-30

Ph2A MD Age 6-11

Phase 1 | Hypothesis Generating Studies | Phase 2

How do we capture this?



I want to let you know how this medication has changed our son's life but also for our family!! His communication skills have sky rocketed!! He is more understandable, talks in complete, lengthy sentences. He has also for the first time been able to self correct his actions and words. This has been a huge step There has been less frustration since he can be understood verbally. And he has liked not having me to interpret for him. What freedom he has had. But to have our extended family tell us that they could understand 90% of what he was saying was awesome!! They could actually carry on conversations of interest!! This made our son feel like a "normal" teenager! This medication that has given him such freedom and confidence. And less stress on us as a family!!

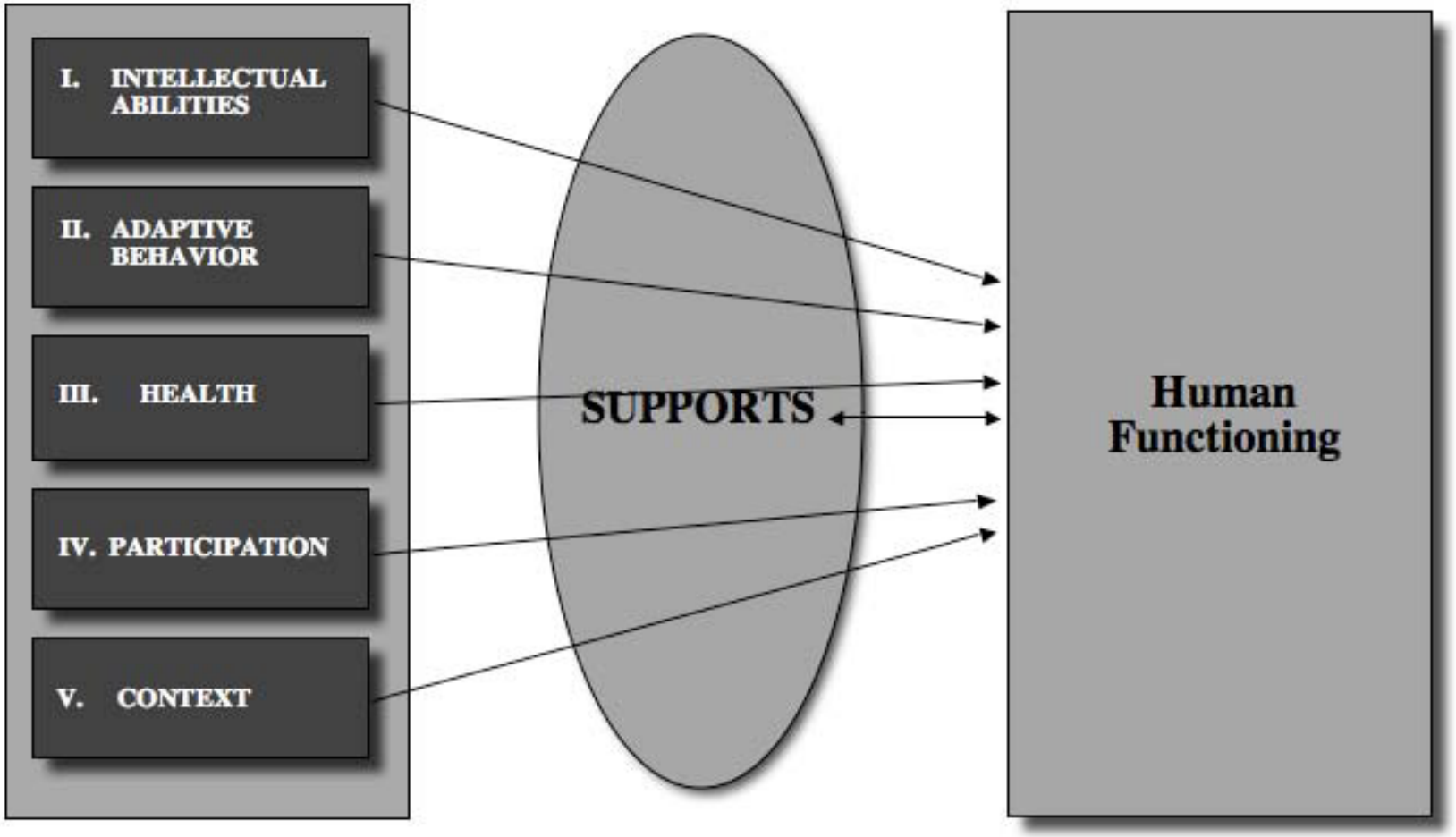
Challenges to PRO selection in DS

- Caregiver and patient **perspectives** in DS
- What is a **meaningful outcome** to measure in this disease condition?
- **Appropriateness** of self-report vs. observer/clinician report in DS
- Do **observer insights** have a role in pediatrics outcomes assessment?
- How should the different insights captured from the **different responders** be reconciled?
- Which one should take **precedence** over the other?

The challenge:

- Participant M, a 16 year old girl with DS was enrolled on study drug X
- Her parents reported marked increase in independent use of language
- She was withdrawn from the study by her parents due to worsening oppositional behavior

Benefit may be paradoxical



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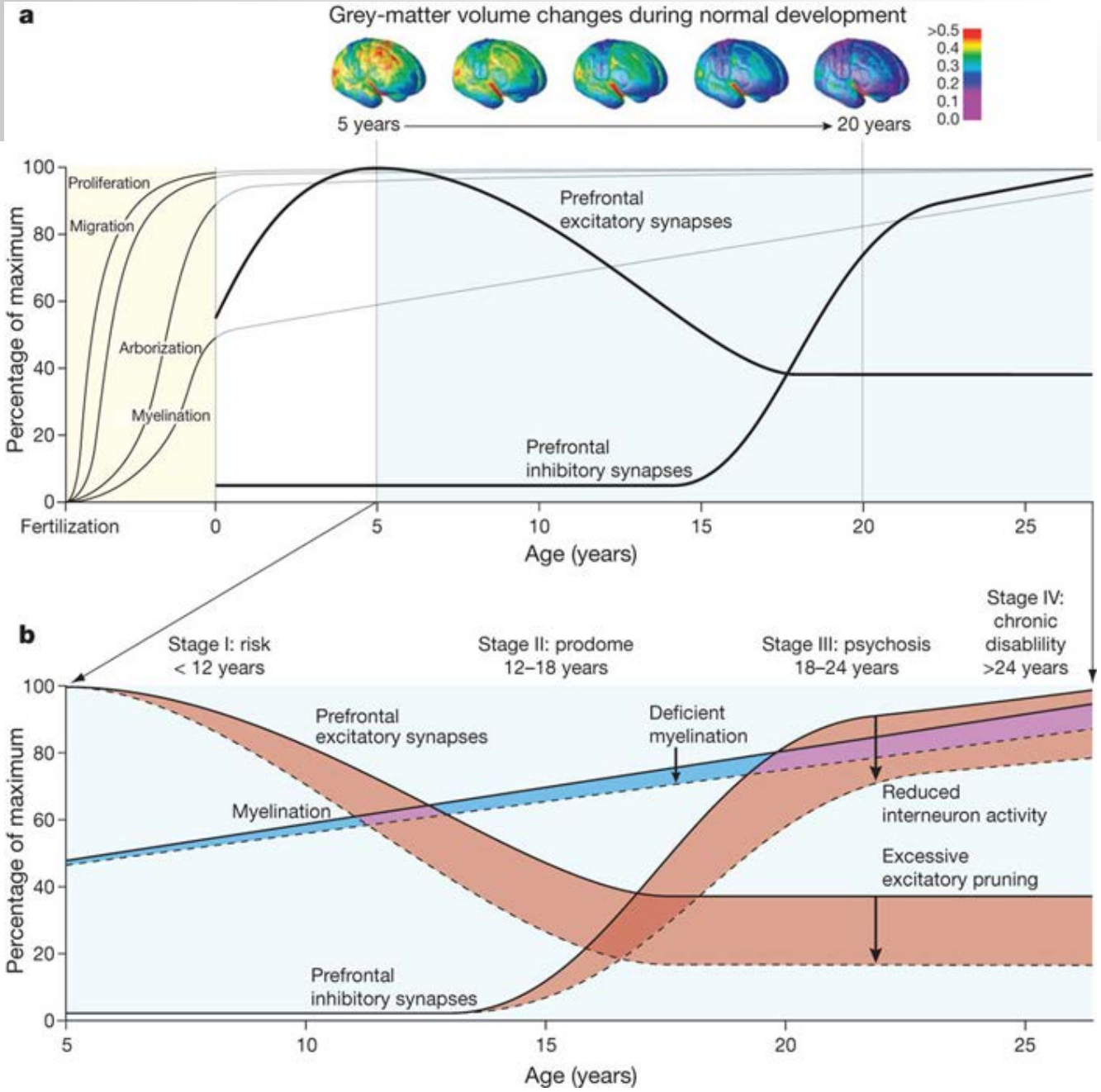
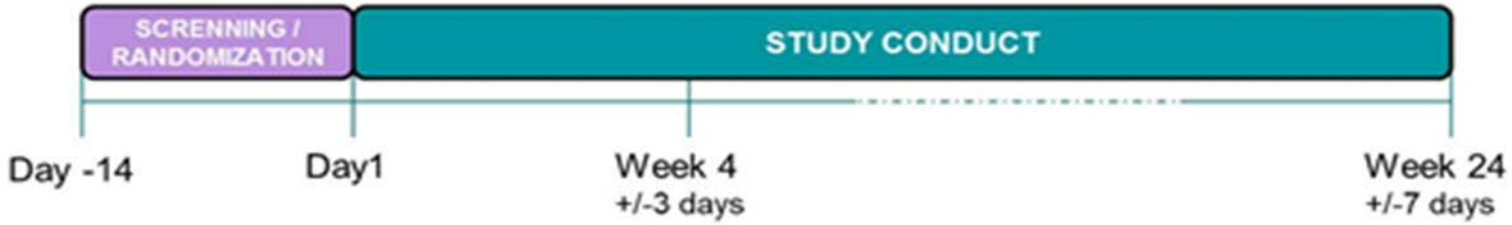


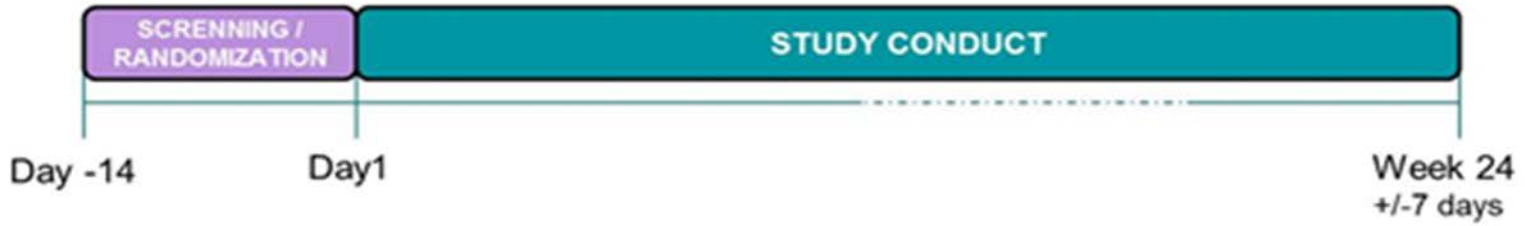
Supporting observational study

Overview of Study BP25612

A multicenter, longitudinal, non-drug study to assess the suitability of neurocognitive tests and functioning scales for the measurement of cognitive and functioning changes in individuals with Down Syndrome



Part 2 (N=30, simplified schedule in additional countries/languages)



Total 90 subjects with Down Syndrome with a tentative balanced number across the age groups [12-17] and [18-30].

CoA Strategy

- To conduct a strategic literature review to further understand the experiences of children and adults with DS and the associated impact on people with DS and carers

- To conduct a review of the adequacy of existing COAs that have been used in studies to date to assess key outcomes in DS

- To provide recommendations regarding which COAs would be suitable to inform a COA endpoint strategy for implementation in clinical trials to assess key outcomes in DS.

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People with DS have functional limitations related to cognition:

For example…

» Difficulty communicating clearly

"My main problem is his communication – speech. He pronounces words very, very badly."

Roche GABA alpha-5 in Down Syndrome Market Research

» Reading difficulties

"X is going into 4th grade and he is still not reading! I feel like we've tried everything but it's just not getting through." ***Downsym.com, 2012***

» Difficulty following instructions

"She doesn't listen very well." ***Graff et al., 2012***

» Short attention span

"It has been noted with myself and of course X's teachers that his attention span is short… if it is something he is interested in he will concentrate longer, however when it comes to other things we have our good and bad days." ***Downsym.com, 2012***

Limitations in DS can have emotional impacts and social/relationships impacts:

For example…

≫ Anger frustration

"She is very aggressive with other children…She will also become enraged when she doesn't get her way. She has recently started trying to destroy property when she is mad." ***Downsym.com, 2012***

≫ Sadness

"He grumbles why I gave birth to him, why his face looks like it does, and why he cannot think and speak well." ***Sari et al., 2006***

≫ Social isolation/withdrawal

"Pupils with DS are found to be at considerable risk of becoming socially isolated as they, in comparison to their peers, show less frequent peer interactions." ***Dolva et al., 2010***

≫ Relationship with family

"He has no control over these behaviours. I'm worried about how this is impacting our family dynamic and how we can continue to function this way." ***Downsym.com, 2012***

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Limitations in DS can have impacts on the carer:

For example…

- **Balancing caregiving with other responsibilities**

  "My dad's taken time off work a lot to go to the doctor with her." ***Graff et al., 2012***

- **Stress**

  "I think it causes a lot of stress, and they're [parents] very patient with her…I think in some ways it's put a stress on their marriage." ***Graff et al., 2012***

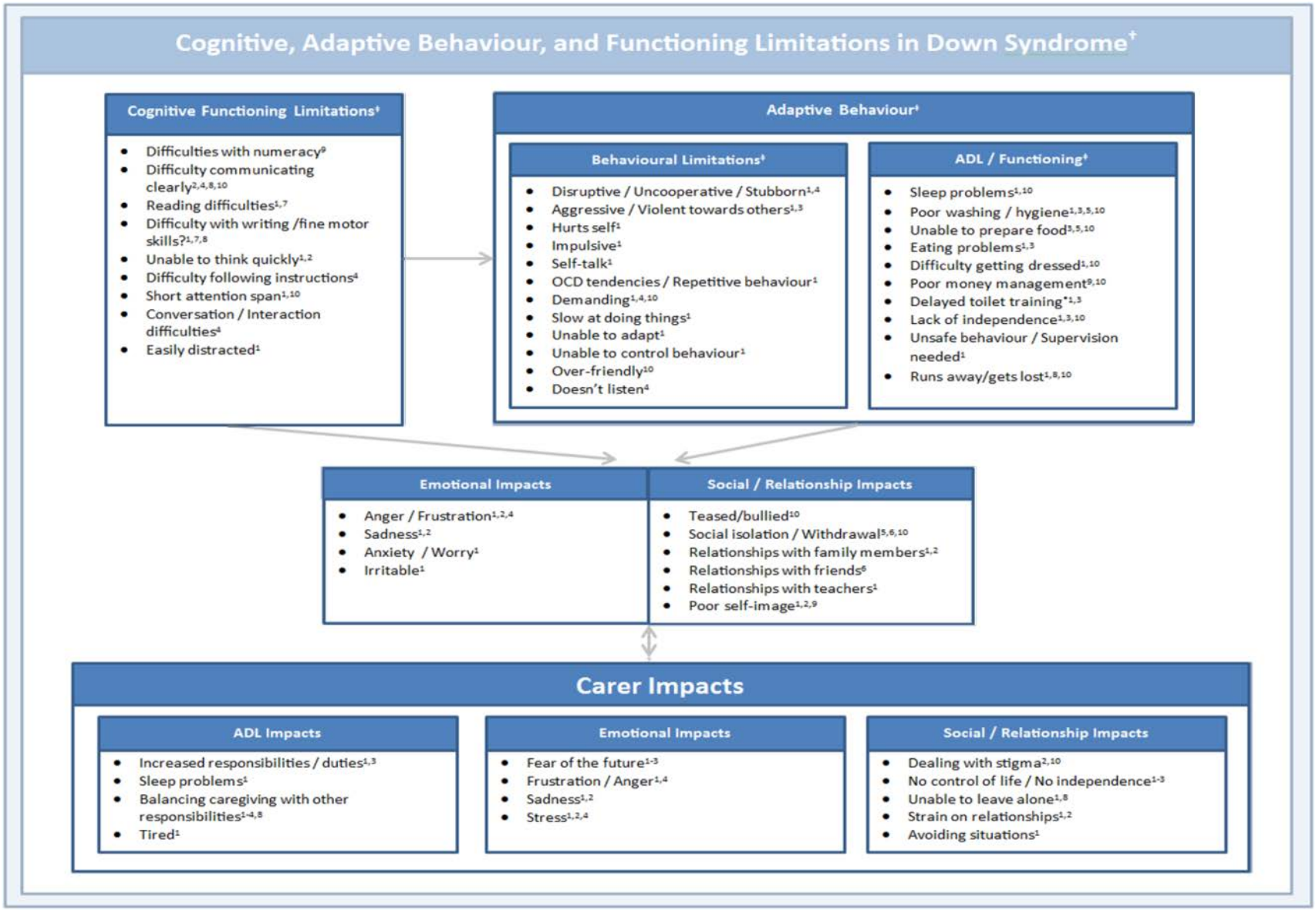
- **No control of life/independence**

  "I don't get any pleasure from life because he is always on my mind." ***Sari et al., 2006***

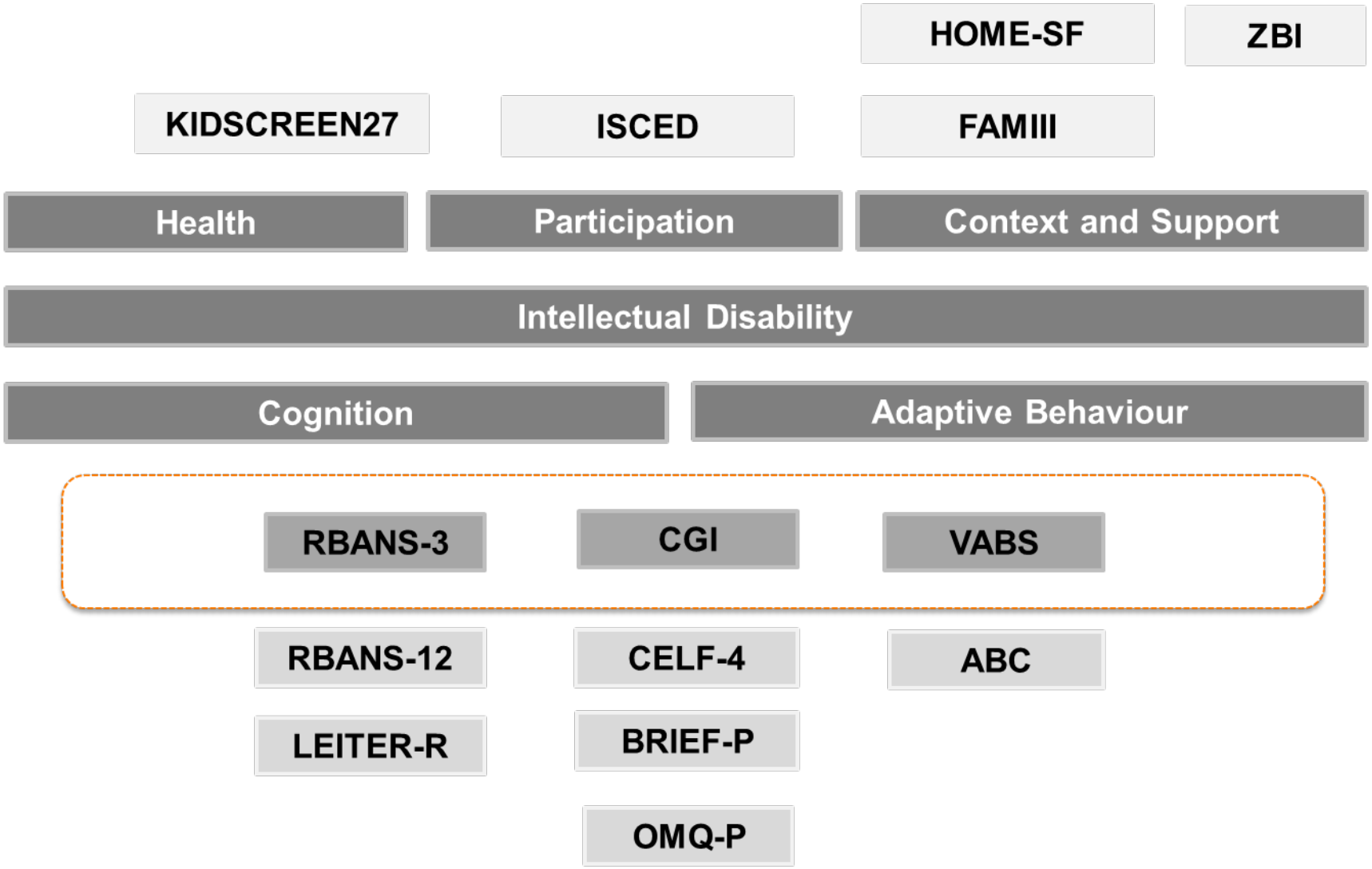
- **Fear of the future**

  "It makes me think way too far ahead in her future…because I see struggles before her, I'm scared of what might happen to her when we are gone." ***Downsym.com, 2012***

Disease model



Conceptual structure of Ph2b

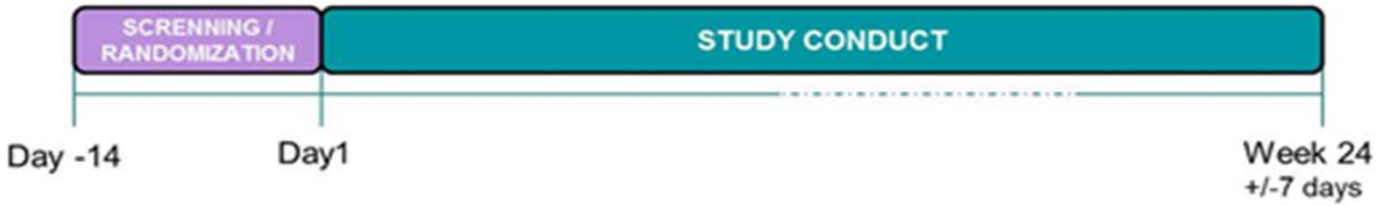


Supporting observational study

Overview of Study BP25612

A multicenter, longitudinal, non-drug study to assess the suitability of neurocognitive tests and functioning scales for the measurement of cognitive and functioning changes in individuals with Down Syndrome

Part 2 (N=30, simplified schedule in additional countries/languages)



Total 90 subjects with Down Syndrome with a tentative balanced number across the age groups [12-17] and [18-30].

Proposal for next steps

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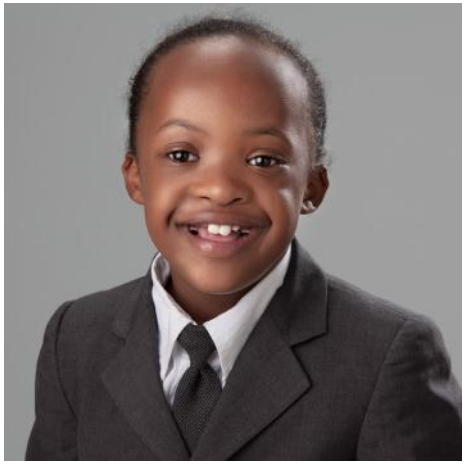

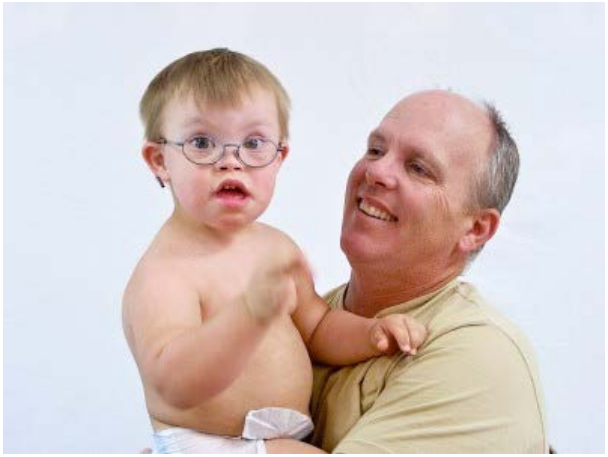

Summary

- Clinical trials for IDD are here
- Major challenges exist for PRO selection and development
  - Different forms of IDD
  - Developmental trajectories
  - How to capture participants' perceptions of benefit
  - How to capture caregivers' perceptions of benefit
  - How establish clinical meaningfulness

Acknowledgments

Acknowledgments

Linda Abetz-Webb and colleagues

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Thank you for your attention!

Discussion and/or Questions?

- Both FDA and EMA have published guidance on the standards that PRO instruments to be used in clinical trials to support product labelling claims (FDA 2009 Guidance for Industry; EMA 2006 Reflection paper).
- Considerations for PROs are also the same for other COAs such as Clinician-Reported Outcomes (ClinROs) and Observer-Reported Outcomes (ObsROs).

PRO aspect	Issues for consideration
Content validity	• Does the instrument adequately capture all concepts that are important to patients and in a way that is easily understood and interpreted consistently by patients? • Level of patient involvement in development of scale? • Has pilot test/cognitive debriefing been conducted? • Confirmation of disease model? • Evidence of saturation?
Item wording	• Are items worded in a manner that is clear and will be consistently interpreted by patients? • Does the wording of the items match the claim being sought?
Response scale structure	• Wording clear? • Represent similar intervals and do not bias the direction of responses? • Appropriate for the intended population?
Recall period	• Appropriate recall period? (dependent on variability, duration, frequency and intensity of the concept measured, characteristics of the disease/condition) • Items with short recall periods generally preferred.
Psychometric Validity	• Does the instrument measure concepts in a reliable and valid manner? This is typically confirmed through the conduct of quantitative studies using the measure in the target population. • Reliability (internal consistency and test-retest) • Validity: Concurrent/convergent, Discriminative validity • Responsiveness

Name of Instrument	No. of Abstracts	Type of COA	Justification for inclusion in the review
Vineland-II Adaptive Behaviour Scales (VABS-II)	6	ObsRO	• One of the most widely used instruments in review of abstracts • Includes parent and teacher ratings • Able to demonstrate change post intervention • Able to demonstrate change between treatment and study/control groups
Adaptive Behaviour Scale (ABS-S:2)	2	ObsRO	• Appropriate age range from 3-18 • Designed to be used in populations with behaviour disorders or intellectual disabilities • Measure of adaptive behaviour
Behaviour Rating Inventory of Executive Function (BRIEF)	1	ClinRO/ ObsRO	• Only identified in one abstract from the literature review, but recommended based on AV experience and widespread use in similar studies.
Scales of Independent Behaviour - Revised (SIB-R)	0	ClinRO	• Not identified in literature review, but recommended for inclusion due to AV experience with the measure.
TNO-AZL Children's Quality of Life questionnaire (TACQOL)	2	PRO/ ObsRO	• Previously been included in a study of DS although it is not clear whether the child-completed or proxy-completed version was used. • Appears to have good content coverage
Parenting Stress Index (PSI/SF)	1	PRO for parents/CGs	• Only carer burden instrument that appeared relevant
Children's Communication Checklist (CCC-2)	1	ObsRO	• Has previously been included in a study of DS. • Includes 2 subscales which consider social aspects of communication. These may be particularly useful in considering adaptive behavior.
Pediatric Evaluation of Disability Inventory (PEDI)	2	ClinRO	• Included in 2 identified studies of DS

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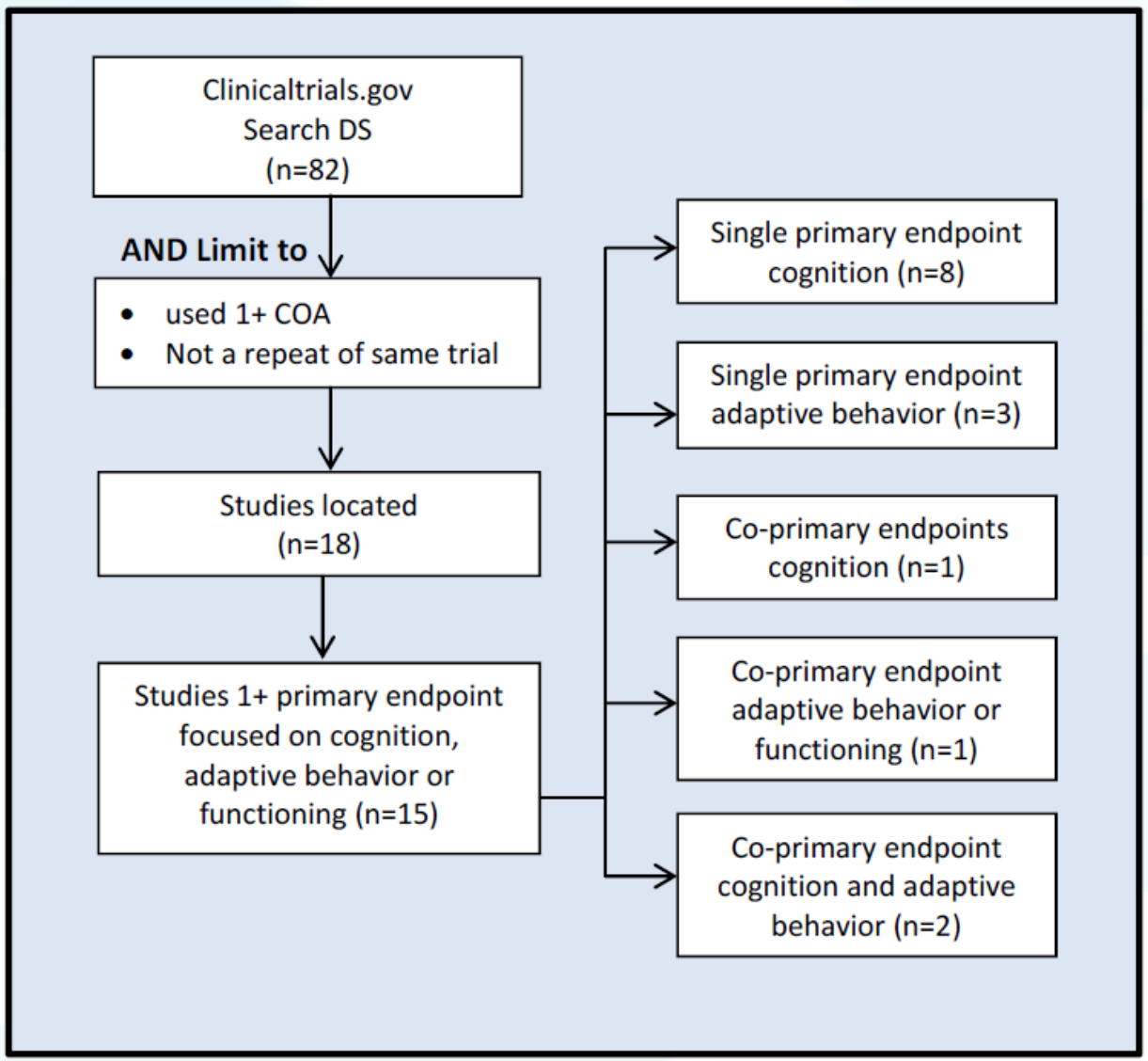
Name of Instrument	Concept coverage							
	Cognitive functioning limitations	Adaptive behaviour: Behavioural limitations	Adaptive behaviour: ADL/ functioning	Emotional impacts	Social relationship impacts	Carer impacts: ADL	Carer impacts: Emotional	Carer impacts: Social/ Relationships
Vineland-II Adaptive Behaviour Scales (VABS-II)	✓	✓	✓	✓	✓			
Adaptive Behaviour Scale (ABS-S:2)	✓	✓	✓					
Behaviour Rating Inventory of Executive Function (BRIEF)	✓	✓	✓	✓				
Scales of Independent Behaviour - Revised (SIB-R)	✓	✓	✓		✓			
TNO-AZL Children's Quality of Life questionnaire (TACQOL)	✓	✓	✓	✓	✓			
Parenting Stress Index (PSI/SF)	✓	✓		✓		✓	✓	✓
Children's Communication Checklist (CCC-2)	✓	✓		✓		✓	✓	✓
Pediatric Evaluation of Disability Inventory (PEDI)	✓	✓	✓		✓			

✓ = Concept covered

Instrument Review Results: Vineland-II Adaptive Behaviour Scales (VABS-II)

Overview	Advantages	Disadvantages
Aim To assess adaptive behaviour from birth to adulthood **Mode of Administration** • Survey interview form and parent/caregiver rating form (20-60 mins) • Expanded interview form (25-90 mins) • Teacher rating form (20 mins) **Age** 0-90 years **Structure** • 4 domains of communication (subdomains: receptive, expressive & written skills), daily living skills (personal, domestic, community), socialisation (interpersonal relations, play & leisure time, coping skills) and motor skills (fine & gross) (383 items). Motor skills typically assessed in children younger than 6. • Optional domain of maladaptive behaviour (internalizing & externalizing) (50 items). For children age 5+ • 3 response options: 'Usually', 'Sometimes/Partially' and 'Never' and 'I don't know option'. • For each subdomain a basal and ceiling rule is defined which guides administration **Scoring** • In each subdomain scoring begins with the item designed for the individuals age.	**Use in DS trials** • From the competitor review, the VABS-II has being used in **5 trials in DS** as predominantly a primary endpoint - e.g. in a study looking at the efficacy and safety of Aricept in treating cognitive dysfunction in children with DS (Pfizer). • Has also been used as a co-primary endpoint in a study of efficacy of Rivastigmine on language and cognitive function in DS (Taiwan University Hospital). **Psychometric validity** Good psychometric properties including: • Internal consistency cronbach's alpha ranging from α=0.80-0.95 across the domains. Adaptive Behaviour Composite α= 0.98. • Test-retest reliability of 0.81-0.86 across the domains. (Time frame not specified). The psychometric information has been sourced from the test publisher and PROQOLID database. Test used was not specified. • Inter-rater reliability ICC=0.62-0.78. • Concurrent validity with the Behavior Assessment System for Children (BASC-2) parent rating form (r=0.34-0.74) • Those with cognitive delay had a mean adaptive behavior composite score two SDs below the mean of the nonclinical group.	**Length of questionnaire** • Ranges from 20-95 minutes to complete depending on the version. **Content validity** • No information available but seems to have been developed using the literature and field tests with carers. • No interviews/observations of children involved. **Recall period** No specified recall period, seems to just rely on 'typical' behaviour at that point in time.


Clinicaltrials.gov
Search DS
(n=82)
AND Limit to
used 1+ COA
Not a repeat of same trial
Studies located
(n=18)
Studies 1+ primary endpoint focused on cognition, adaptive behavior or functioning (n=15)
Single primary endpoint cognition (n=8)
Single primary endpoint adaptive behavior (n=3)
Co-primary endpoints cognition (n=1)
Co-primary endpoint adaptive behavior or functioning (n=1)
Co-primary endpoint cognition and adaptive behavior (n=2)

Outcome Measures for Clinical Trials: Individuals with Intellectual and Developmental Disabilities (IDD)

Tiina K. Urv, Ph.D.
Eunice Kennedy Shriver **National Institute of Child Health and Human Development**

FOURTH ANNUAL
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

April 25, 2013 ■ Silver Spring, MD

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Background

- The views expressed in this article are those of the authors and do not necessarily represent the views of the NIH or the United States Government.

Background

- For years scientists have sought to alleviate the debilitating cognitive, behavioral, and comorbid medical symptoms associated with Intellectual and Developmental Disabilities (IDD) such as:
  - **Down syndrome**
  - **Fragile X syndrome**
  - **Rett syndrome**
  - **Angelman syndrome**
  - **Prader-Willi syndrome**
  - **autism spectrum disorders**
- In recent years progress in basic research has led to identification of underlying mechanisms in several neurodevelopmental disorders that have led to trials for therapeutics.
- While this progress is highly encouraging it has become evident that there is a gap in the ability to translate to targeted therapies to humans effectively.
- One major obstacle to the demonstration of efficacy in human trials in individuals with IDD has been the lack of generally accepted endpoints to assess improvement in function.

Challenges related to assessing individuals with IDD

- Display broad range cognitive abilities
- Behavioral challenges
- Broad age range
- Comorbid conditions
  - Sensory impairments
  - Physical impairments
- While standardized assessments for individuals with IDD exist are they sensitive enough for clinical trials?

Current trials

- New knowledge from studies of translational models of IDD, as well as genetic, imaging and neuropsychological investigations of people with IDD has opened the door to disease-specific pharmacological treatment approaches
  - For most disorders disease-specific interventions have not been approved
- There are a number of symptom-based pharmacological treatments available to treat individuals
  - Open-label pilot trials & small pilot placebo controlled double blind trials.

Challenges related to existing trials

- Limited available data regarding the efficacy of interventions
- Clinical endpoints often differ across trials
- Adequacy of outcome measures not clear

Series of Outcome Measures Meeting

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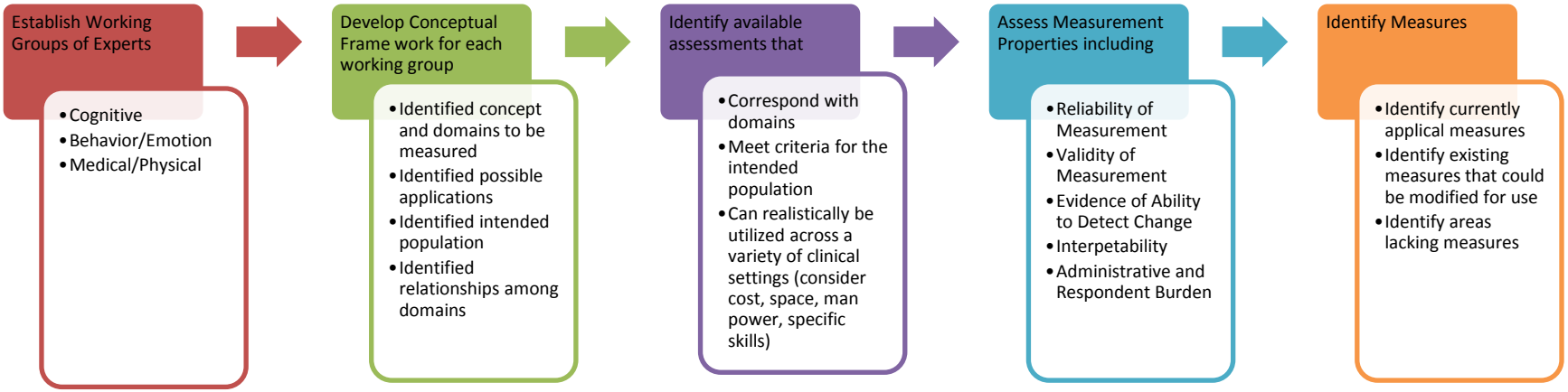

Activities completed through a series of virtual meetings

Two day Face-to-face meeting

Process for developing recommendations for the optimal outcome measures - based on FDA *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*

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Series of Outcome Measures Meetings Targeting Fragile X syndrome

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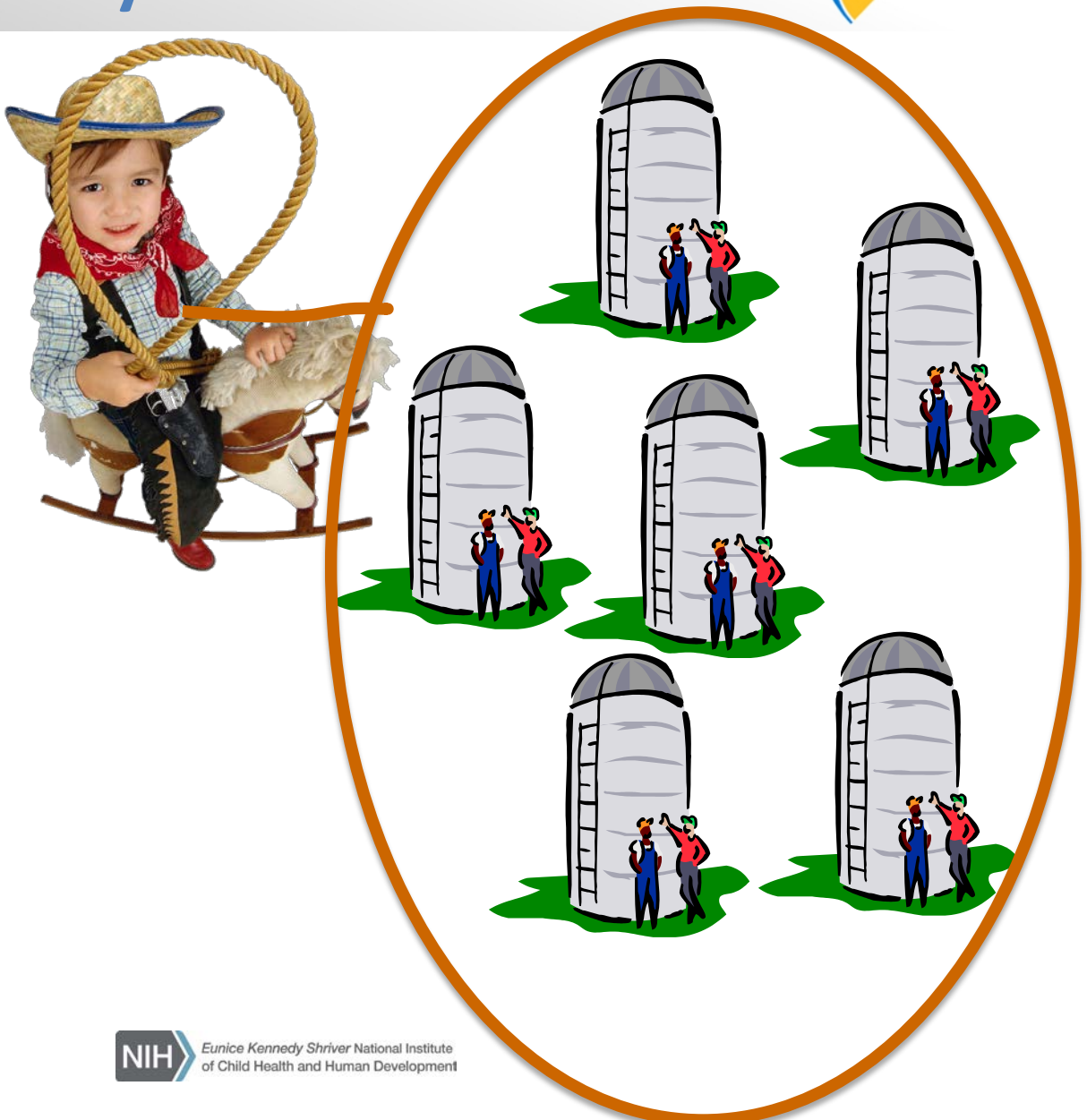
Participants included experts from:

- Multiple disciplines related to Fragile X syndrome
- Design and implementation of clinical trials
- Measurement development,
- Representatives of pharmaceutical industry
- Constituency groups
- Relevant federal agencies



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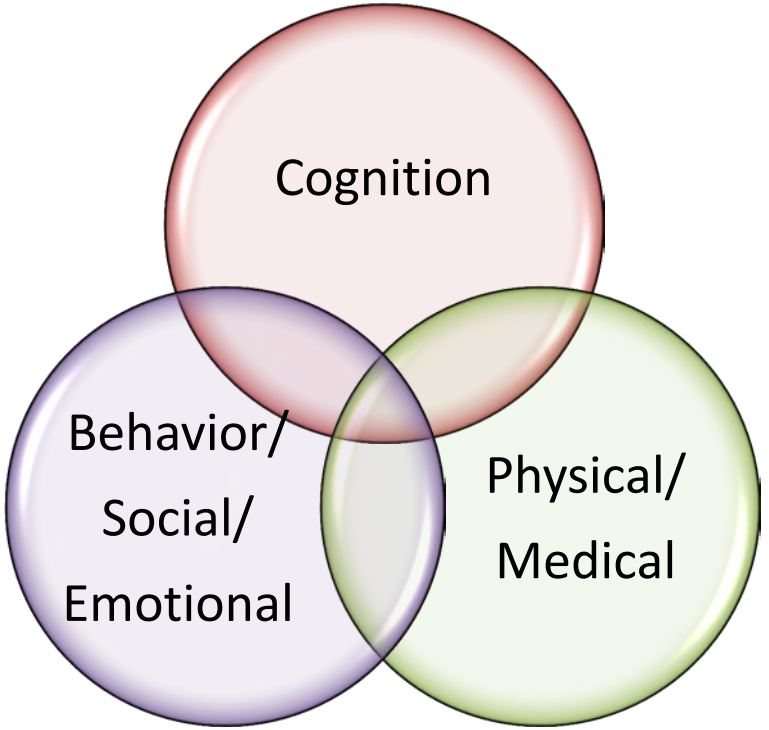
Establish Working Groups

- Cognitive
- Behavior/Emotion
- Medical/Physical



Develop Conceptual Framework for each working group

- **Identified concept and domains to be measured**
- **Identified possible applications**
- **Identified intended population**
- **Identified relationships among domains**

- Biomarkers and Medical Measures
  - Blood and Tissue Biomarkers
  - Electrophysiological Measures
  - Eye Tracking and Pupilometry
  - Neuroimaging Studies

- Cognition Language
  - Memory and Learning
  - Executive Functioning
  - Social Cognition
  - Academic Achievement

- Behavior and Emotion
  - Inattention
  - Hyperactivity/Impulsivity
  - Irritability/Aggression
  - Self-injury
  - Anxiety
  - Repetitive/Compulsive behavior
  - Sleep problems
  - Social Avoidance

Identify available assessments that:

- Correspond with domains
- Meet criteria for the intended population
- Can realistically be utilized across a variety of clinical settings (consider cost, space, man power, specific skills)

Subdomain/Measure	Administration Time/ Requirements	Strengths	Weaknesses
Language Standardized Language Sampling Procedures • Conversation • Narration • Structured play	20 min.	Allows characterization of a wide range of functional language behaviors; can be adapted for a wide-range of ability levels	Labor-intensive in terms of transcription requirements; psychometric properties not fully known Unknown psychometric properties
Fast Mapping	10 min.	Process-based; applicable across a wide range of ability levels	
Memory WJ Auditory Working Memory WJ Digits Reversed Corsi Blocks CANTAB Object Memory RBANS List Learning	5 min. 5 min. 5 min. 10 min 5-15 min.	Broad coverage; good psychometric properties in general population; evidence of reliability and validity in FXS	Not all subtests appropriate for lower-functioning people, especially Digits reversed and List Learning
Executive Function WJ Planning Contingency naming KiTAP (4 subtests) WJ Rapid naming	5-10 min. 5 min. 20 min. 5 min.	Broad coverage; good psychometric properties in general population; evidence of reliability and validity in FXS	Not all subtests appropriate for lower-functioning people, especially those with limited language

Assess Measurement Properties including:

- Reliability of Measurement
- Validity of Measurement
- Evidence of Ability to Detect Change
- Interpretability
- Administrative and Respondent Burden

Identify Measures

- Identify currently applicable measures
- Identify existing measures that could be modified for use
- Identify areas lacking measures

J Autism Dev Disord (2012) 42:1377–1392
DOI 10.1007/s10803-011-1370-2

ORIGINAL PAPER

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1R01HD074346-01A1

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PREVIOUS Project 4 of 4

DESCRIPTION | DETAILS | RESULTS | HISTORY | SUBPROJECTS | SIMILAR PROJECTS | NEARBY PROJECTS BETA | LINKS | NEWS AND MORE

Project Number: 1R01HD074346-01A1
Title: EXPRESSIVE LANGUAGE SAMPLING AS AN OUTCOME MEASURE
Contact PI / Project Leader: ABBEDUTO, LEONARD J
Awardee Organization: UNIVERSITY OF CALIFORNIA DAVIS

Abstract Text:

DESCRIPTION (provided by applicant): New treatments for people with intellectual disabilities (ID) are increasingly condition-specific in nature. Numerous clinical trials of targeted pharmacological agents are now in process for fragile X syndrome (FXS) and Down syndrome (DS). Condition-specific behavioral treatments also are emerging. Evaluation of all such treatments is being hampered by a lack of adequate cognitive and behavioral endpoints. In this project, we propose to evaluate the adequacy of expressive language sampling for deriving language-relevant clinical endpoints. In this procedure, expressive language samples are collected in highly structured and scripted, yet naturalistic, interactions. These samples can then be analyzed to derive clinical endpoints reflecting important dimensions of language skill and atypical language behavior. Although the suitability of expressive language sampling for clinical trials with FXS or DS (or ID more generally) has yet to be determined, the procedures are especially promising because they yield clinically relevant and functional endpoints, have been shown to capture impairments that are common to ID as well as those specific to FXS or DS, and have been shown to yield robust indicators of developmental change within typical and other language-impaired populations. In this project, we propose: (1) to examine the basic psychometric properties of measures derived from expressive language sampling techniques, including establishing their test-retest reliability, internal consistency, validity, and sensitiviy; (2) to evaluate differences in the psychometric properties of expressive language sampling techniques as a function of variations in participant etiology, age, gender, autism symptom severity, and level of ID; (3) to compare the psychometric properties of three different expressive language sampling techniques; and (4) to evaluate the feasibility of implementing the expressive language sampling across multiple sites, as would be required in a typical clinical trial. These aims will be addressed by collecting expressive language samples from children, adolescents, and young adults with FXS or DS. Samples will be collected within three interaction formats: conversation, narration, and the structured interactions comprising the Autism Diagnostic Observation Schedule (ADOS). Measures derived from the samples will include those indexing syntax (an area of especially severe impairment in DS) and perseveration (an area of especially severe impairment for FXS). Test-retest reliability will be assessed at 4 weeks (+/- 1 week) using alternate versions of sampling materials. Internal consistency will be assessed by computing alpha coefficients within and across sampling techniques. Standardized tests and informant report will be used as indicators of validity. A two-year longitudinal follow-up will yield an estimate of sensitivity to change. Participants will be tested at multiple sites, each with considerable experience in the evaluation of individuals with FXS or DS. Feasibility of multiple-site implementation will be evaluated by comparing language samples across sites on key indicators. Transcription, coding, and analysis will be conducted only at the UC Davis MIND Institute site. PUBLIC HEALTH RELEVANCE: New pharmaceutical and behavioral treatments for people with intellectual disabilities (IDD) are increasingly condition-specific in nature. Evaluation of al such treatments, however, is hampered by the lack of adequate cognitive and behavioral endpoints. In this project, we propose to evaluate the adequacy of expressive language sampling for deriving language-relevant clinical endpoints. We focus on fragile X syndrome and Down syndrome, which are the conditions at the center of the development of exciting new treatments.

A portion of the data was presented at the 44th Annual Gatlinburg Conference, San Antonio, TX, in March 2010.

Electronic supplementary material The online version of this article (doi:10.1007/s10803-011-1370-2) contains supplementary material, which is available to authorized users.

caused by the expansion of a trinucleotide repeat sequence, cytosine-guanine-guanine (CGG), in the promoter region of the Fragile X Mental Retardation 1 gene (*FMR1*) on the long arm of the X chromosome at Xq27.3. Expansions

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Thoughts

- Is there a single battery of measures that would be appropriate for all clinical trials for a specific disorder?
  - Unlikely – however, identification of a core set of applicable measures would facilitate comparability across different agents, sites and approaches.
- Don't wait too long to identify or modify existing measure – it will take longer than you think.
- Collaboration, collaboration, collaboration

Acknowledgements

- Elizabeth Berry-Kravis MD
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- Leonard Abbeduto PhD
- Allan L. Reiss MD
- Andrea Beckel-Mitchener PhD
- Tiina K. Urv PhD

Outcome Measures Working Group Participants

Behavior Work Group*:* Michael Aman, Katie Clapp, Scott Hall, David Hessl, Becky Kronk, Ave Lachiewicz, Robert Noll, Lawrence Scahill

Cognition Work Group: Leonard Abbeduto, Elizabeth Berry-Kravis, Heather Cody Hazlett, Stephen Hooper, Bryan King, Amy Lightbody, Richard Paylor, David Posey, Paul Wang, Becky Zorovic

Medical/Physical Work Group*:* Craig Erickson, Randi Hagerman, Walter Kaufmann, Eric Klann, Joseph Piven, Allan Reiss, Linmarie Sikich, Nicole Tartaglia, Michael Tranfaglia

Current Initiative

- **Outcome Measures for Use in Treatment Trials for Individuals with Intellectual and Developmental Disabilities (R01)**
  - Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH)
  - Encourages Research Project Grant (R01) applications from institutions/organizations that propose to develop informative outcome measures for use in clinical trials for individuals with intellectual and developmental disabilities (IDD).
  - This funding opportunity will address a significant need in the field, one that is especially apparent in efforts to develop pharmacological treatments for these populations.
  - This solicitation will focus ongoing clinical and translational research on a neglected area essential for therapy and pharmacological treatment development

Discussion and/or Questions?