

# **Addressing Key Challenges in Developing, Testing and Implementing Clinical Outcome Assessments in Pediatric Trials**

***SEVENTH ANNUAL  
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP***

**April 27 - 28, 2016 ■ Silver Spring, MD**



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# Challenges in Pediatric COA development



- Defining and operationalizing health across a broad spectrum of ages
  - Different measures and reporters
  - Pooling data?
- Engaging children in measure development
- Capturing deceleration as well as deterioration, particularly in early stages of development
- Parent reports vs child report

# Session Outline/Objectives

- To understand the key challenges associated with developing, testing, and implementing clinical outcome assessments in pediatric populations
- To learn different approaches for overcoming these challenges based on real-world case studies
- What has worked and not worked for YOU?

## Moderator

- *Linda Abetz-Webb* – Senior Research Director, CEO, Patient-Centered Outcome Assessments

## Presenters

- *Linda Lowes, PhD* – Nationwide Children’s Hospital, Columbus, OH
- *Rob Arbuckle, MA, MSc* – Vice President and Managing Director, Patient-Centered Outcomes, Adelphi Values
- *Valdo Arnera, MD* – Scientific Advisor and General Manager ERT Geneva

## Panelists

- *Laura Lee Johnson, PhD* – Associate Director, Division of Biometrics III, Office of Biostatistics, Office of Translational Sciences, CDER, FDA
- *Andrew E. Mulberg, MD, FAAP, CPI* – Deputy Director, Division Gastroenterology and Inborn Error Products (DGIEP), OND, CDER, FDA
- *Josephine Norquist* – Patient-Reported Outcomes Specialist, Merck Sharp & Dohme, Corp.
- *Anna Rydén, PhD* – Director, Patient Reported Outcomes, AstraZeneca

# Pediatric point to ponder

*Linda Abetz-Webb –*

Paediatric PRO Expert, CEO/Senior  
Research Director, Patient-Centered  
Outcome Assessments, Ltd.

# Pediatric point to ponder: Are children just another culture?

- Can we learn from linguistic validation by ensuring conceptual equivalence for concepts that are the same (but operationalized differently) across ages:
  - Within reporters?
  - Across reporters, given that parents and children report differently dependent on concepts?
- If we can, can we then pool the data across the age groups just like pooling across languages/cultures?
  - Endpoint development is key.

# Case Studies – How have people dealt with the key challenges in Pediatric COA research?



- Linda Lowes
  - ACTIVE Kinect case study: How do you engage children in the development and refinement of a pediatric performance outcome assessment?
- Rob Arbuckle
  - Functional constipation/IBS-C case study: How do you pool data across age ranges? Use of the same items to assess symptoms across ages using different instrument administrators.
- Rob Arbuckle
  - Common cold case study: Use of a pediatric PRO instrument to assess symptoms in children, adolescents and adults and evaluate if the severity and trajectory of symptoms is comparable across those age ranges.
- Valdo Arnera
  - What are the challenges and solutions when implementing electronic outcome assessments in multinational, pediatric clinical trials?



# Development of a functional outcome measure for Duchenne Muscular Dystrophy

Linda Pax Lowes, PhD, PT

[Linda.Lowes@nationwidechildrens.org](mailto:Linda.Lowes@nationwidechildrens.org)

Nationwide Children's Hospital

# Our Goal: Maximize Recruitment Pool for Pediatric Rare Disease Trials

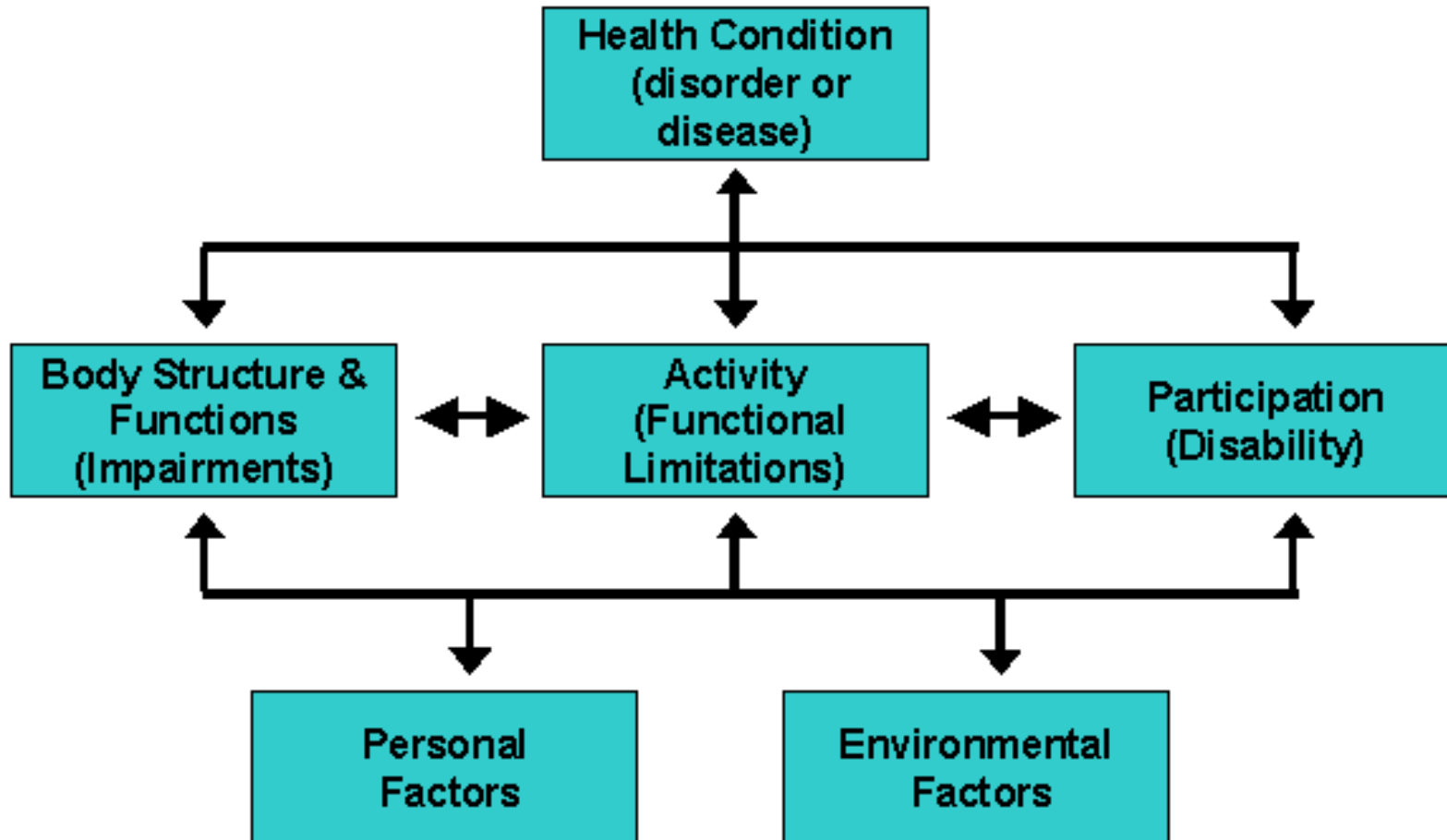


- Duchenne Muscular Dystrophy
  - X linked progressive degenerative genetic disease
  - Rare disease made rarer by individual mutations
  - No cure
  - Fatal by 30
- Exon Skipping Clinical Trial
  - Must walk 6 minutes
  - Not too fast and Not too slow
  - One brother qualified

# What do you think you will impact?

(Rather than what has been used before)

Exon skipping – should make a shorter dystrophin protein

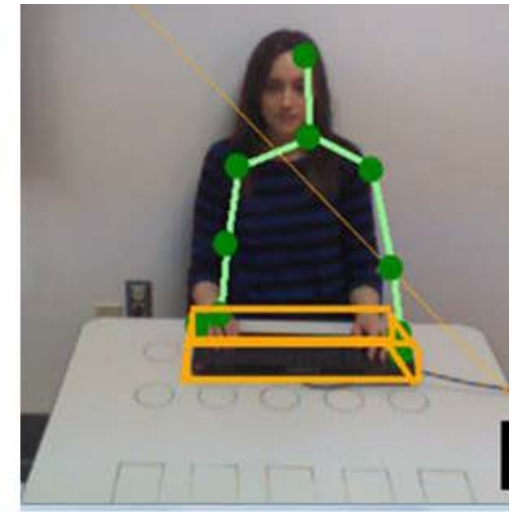
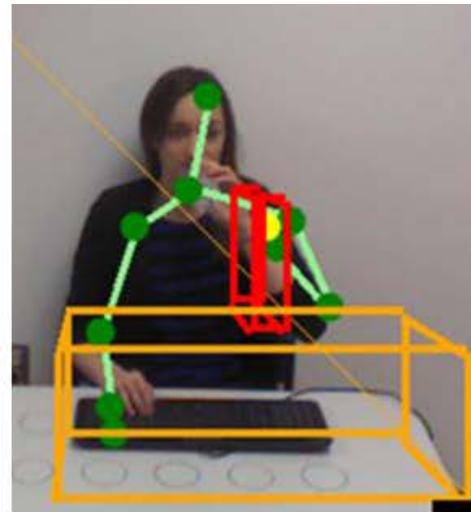
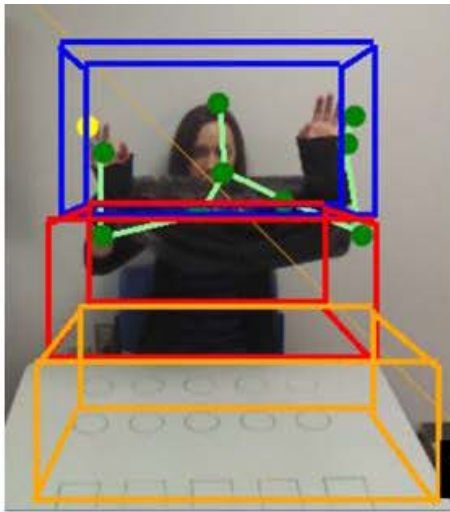


Source: [www.who.int/classifications/icf/site/beginners/bg.pdf](http://www.who.int/classifications/icf/site/beginners/bg.pdf)

- Proximal to Distal Progressive Weakness
- Gower's sign demonstrates early trunk weakness
- Arm Function remains longer than walking ability
  - Traditional tests
    - dexterity,
    - “normal” movement patterns
    - isolated impairments such as strength or flexibility

# Functional Reaching volume

## Real Life Implications



Task: Donning Shirt

Eating/Drinking

Typing

FRV: 0.385 m<sup>3</sup>

0.0631 m<sup>3</sup>

0.008 m<sup>3</sup>

# How do you measure the ability to interact with your environment?

- More than range of motion or strength in isolation
- Must Include Arms and Trunk
- Must Allow Compensations
- Must be Able to Standardize
  - Early efforts included time to don shirt
- Must be motivating for young boys, teens and men

# Human Performance is Variable

Testing Kids is Like Trying to Nail Jell-O to a Tree



I DON'T WANT TO GO TO  
SCHOOL! I HATE SCHOOL!  
I'D RATHER DO **ANYTHING**  
THAN GO TO SCHOOL!



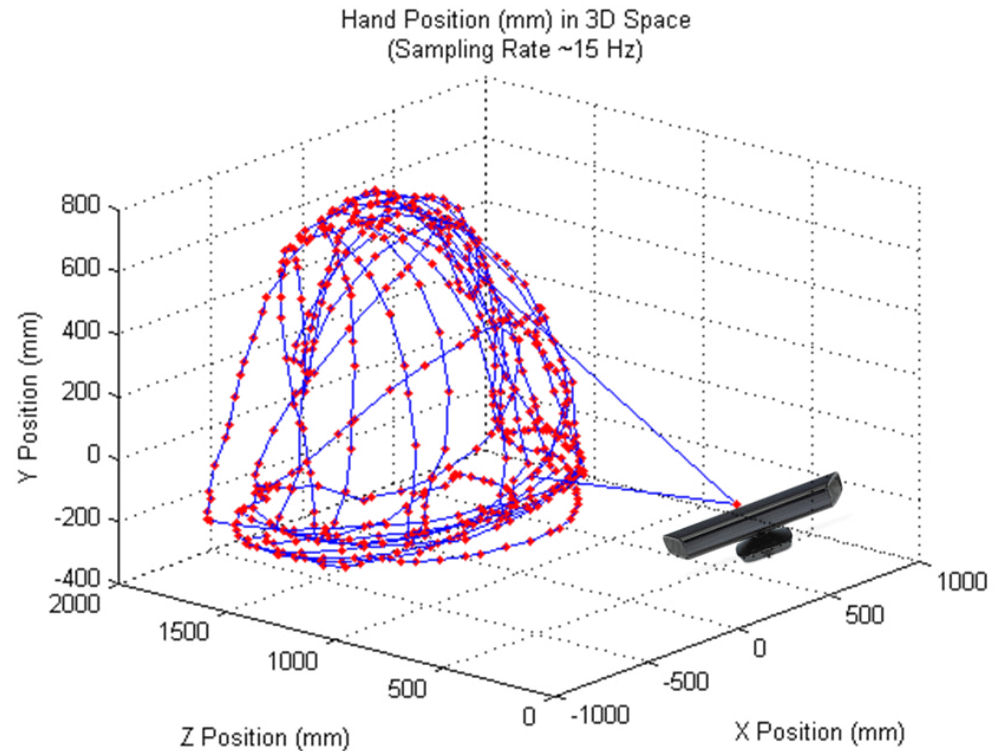
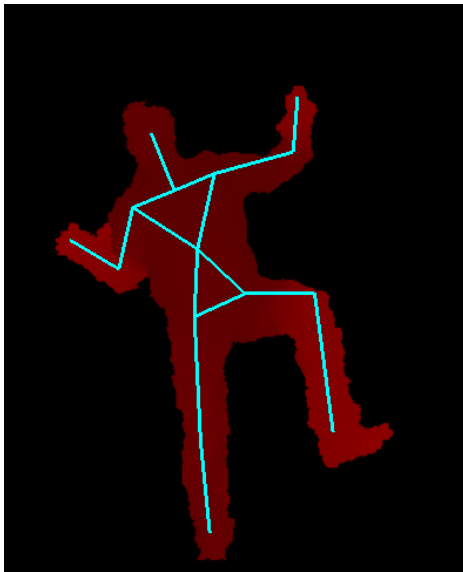
# Need consistent motivation for boys, teens and men



## VIDEO GAMES

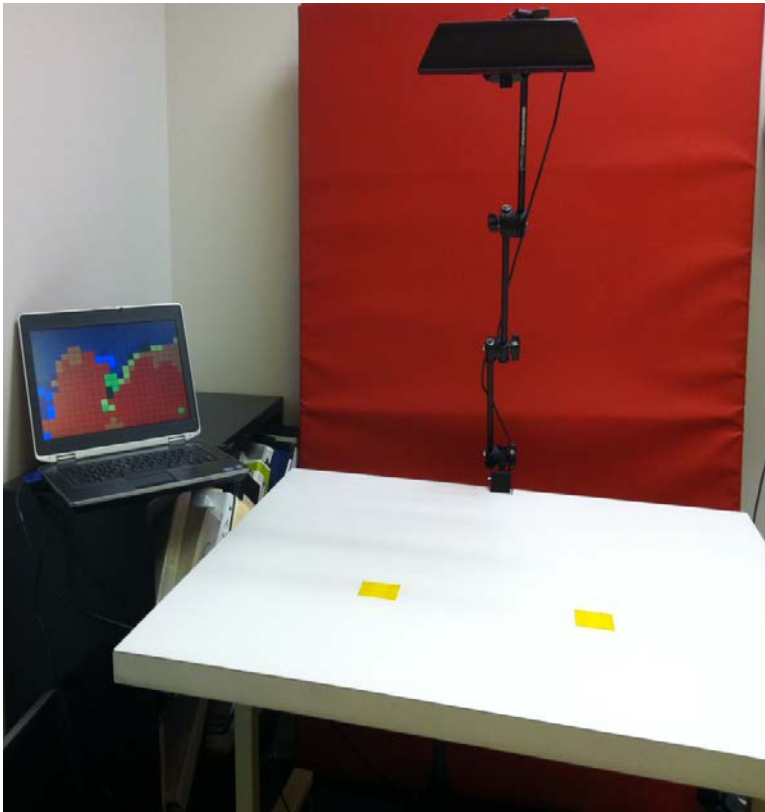


- Started with Accelerometers
- Microsoft Kinect
  - Skeletal tracking
  - Depth
  - RGB color



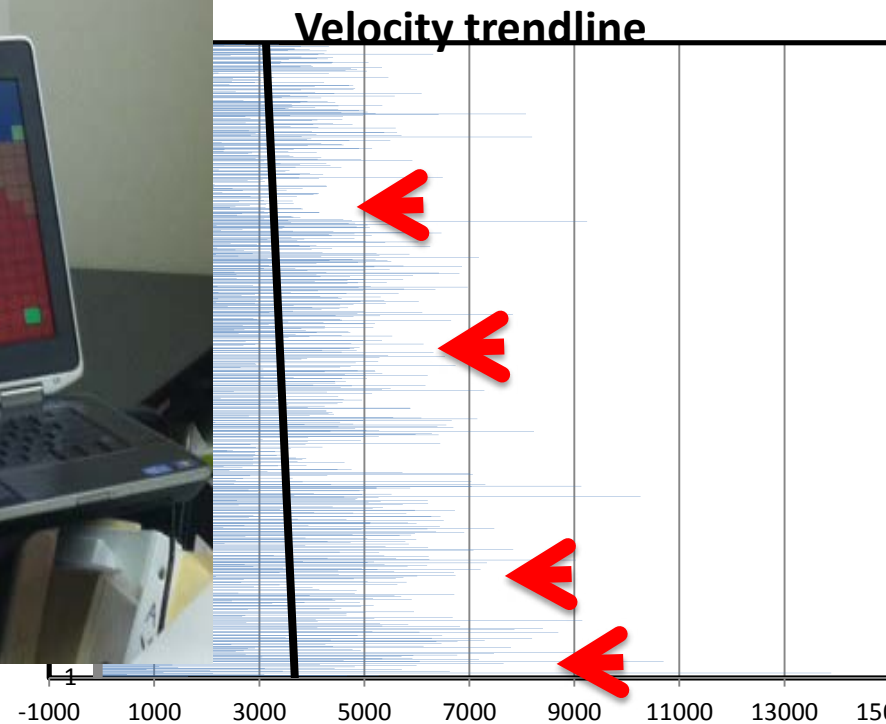
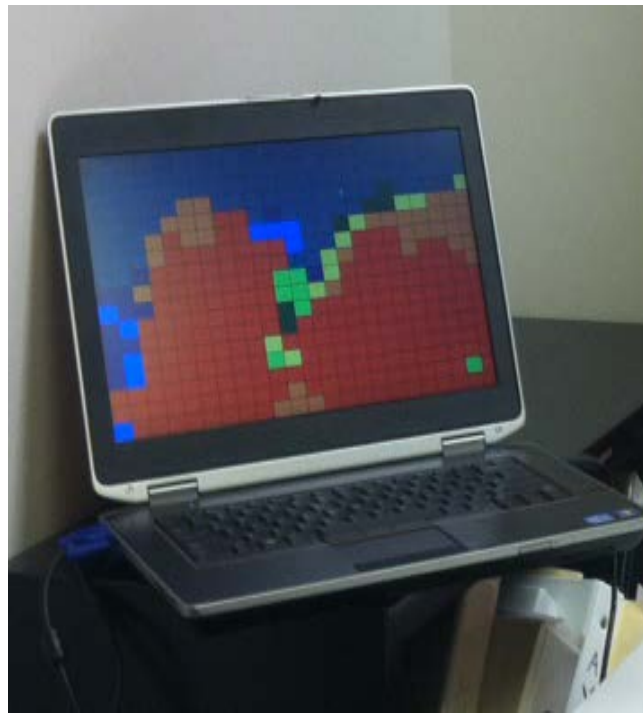
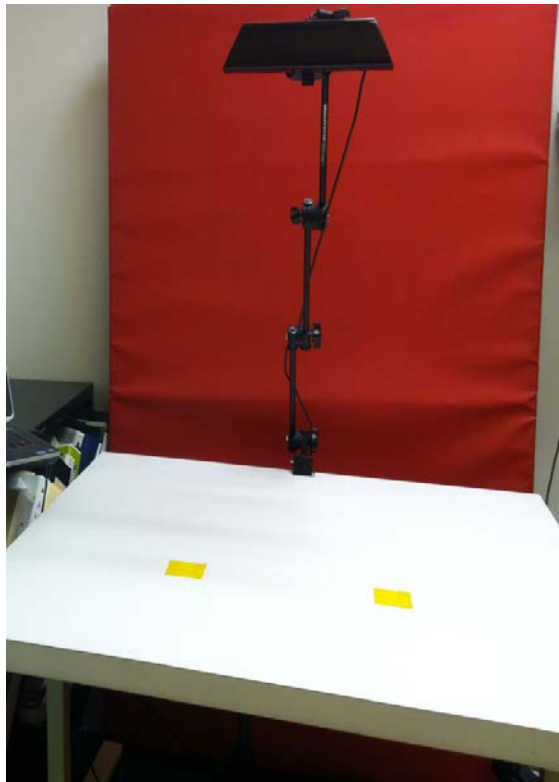
# Prototype 1

Microsoft Kinect v1  
2D Coloring Volume  
“Whack a Mole” Velocity



# Prototype 1

Microsoft Kinect v1  
2D Coloring Volume  
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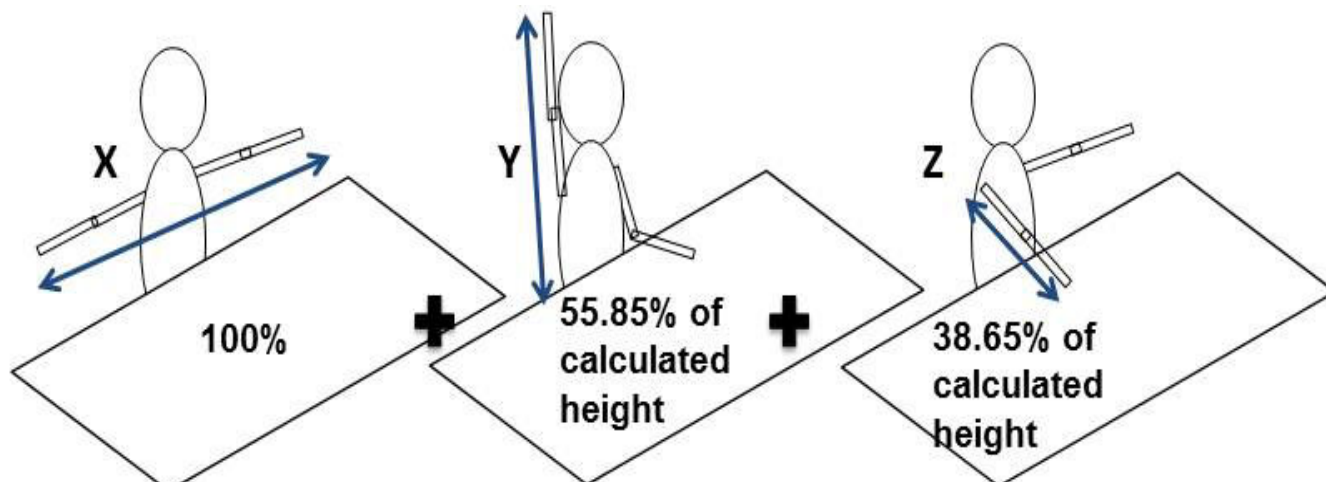


# Issues that could impact reliability



- Kids grow

## Predicted FRV



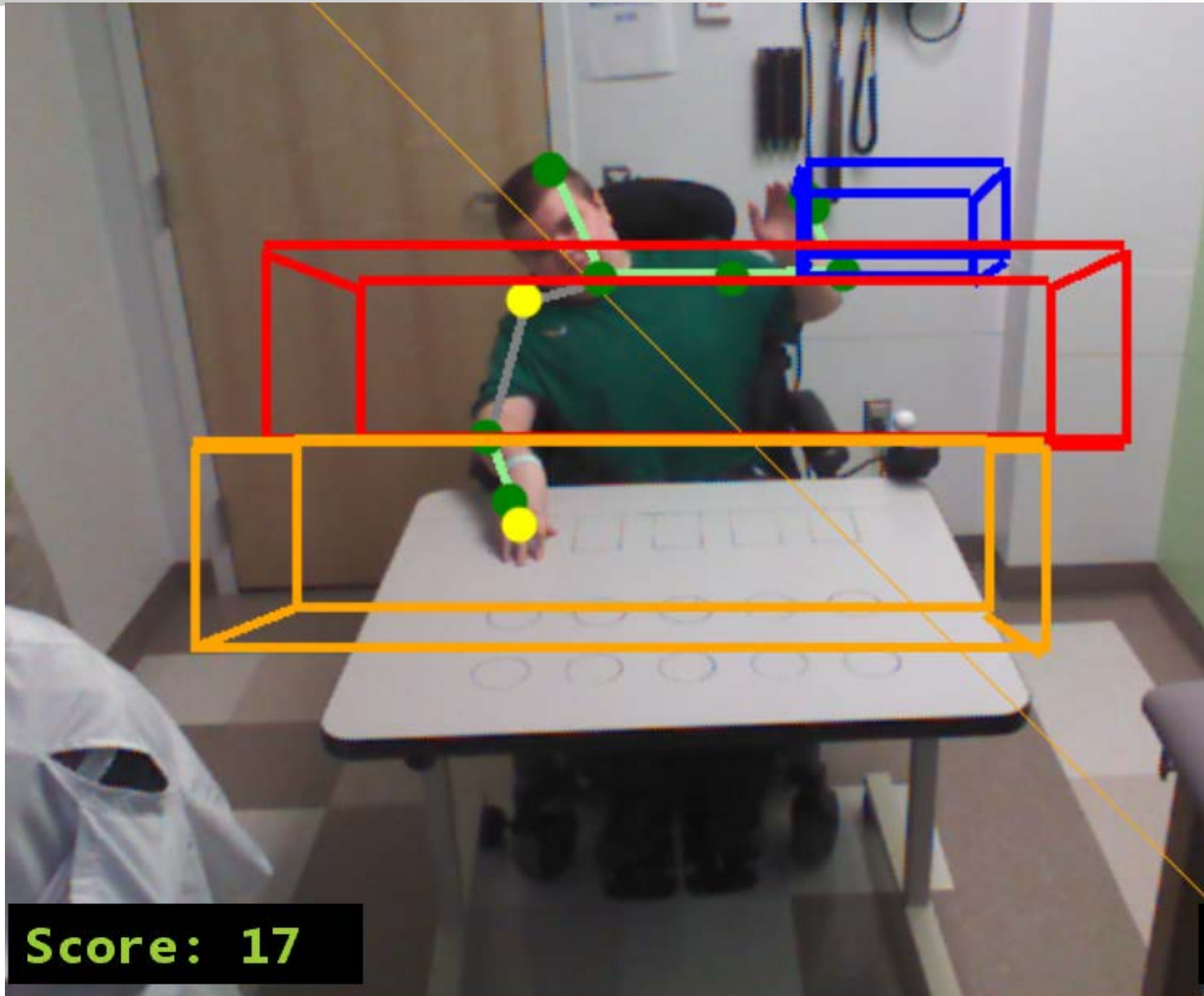
## Percentage of Predicted FRV

$$ppFRV = [(raw\ FRV) / (predicted\ FRV)] * 100$$

- If the subject can lean while reaching score is well over 100%.
- Poor trunk control/limited antigravity movement gives score <100%.

- Kids grow
- Higher incidence of learning disorders

# Version 2- Expanding Boxes



**Score: 17**

- Kids Grow
- Higher incidence of learning disorders
- “Pre-symptomatic” to limited hand function
- Motivation must be standardized



- Survey of Boys with DMD in Clinic



# ACTIVE: Abilities Captured Through Interactive Video Evaluation



- Kids Grow
- Higher incidence of learning disorders
- “Pre-symptomatic” to limited hand function
- Motivation must be standardized
- Equally fun for all abilities
  - Scale by Brooke Level

- Kids Grow
- Higher incidence of learning disorders
- “Pre-symptomatic” to limited hand function
- Motivation must be standardized
- Equally fun for all abilities
  - Scale by Brooke Level
- Are we getting the subject’s maximum ability?
  - 45,60, 90 seconds

60 seconds	45 seconds	Percent Change
0.48	0.47	2.08%
0.96	0.97	-1.04%
2.98	2.46	17.45%
0.75	0.70	6.67%
0.77	0.69	10.39%
0.50	0.51	-2.00%
0.41	0.26	36.59%
1.69	1.88	-11.24%
0.45	0.39	13.33%
0.16	0.13	18.75%
0.64	0.79	-23.44%
1.61	1.80	-11.80%
	Mean:	4.64%

- Initial Briefing Package to Drug Development Tools (DDT) Qualification Programs
- Clinical Outcome Assessment Qualification Program

# **Functional constipation and irritable bowel syndrome with constipation (IBS-C) case study: developing a symptom diary for use across ages 6-17**

*Rob Arbuckle*

Vice President and UK Managing  
Director, Patient-Centered Outcomes,  
Adelphi Values

# Acknowledgements

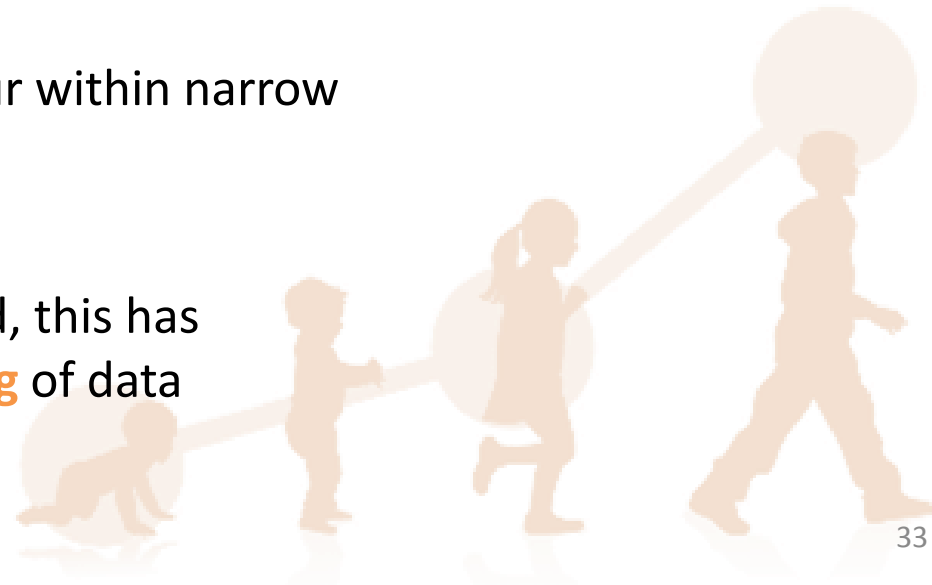
- As always, the research presented here was a huge team effort. The following were all highly involved:
  - Robyn Carson, Jessica Buono from Allergan
  - Mollie Baird\*, Barbara Lewis\*, Jennifer Hanlon and David Reasner from Ironwood
  - Linda Abetz-Webb\* and Kate Bolton\* from Adelphi Values
  - The expert advisors: Jeffery Hyams, Carlo Di Lorenzo and Lynn Walker
  - Many others from the inter-disciplinary teams within each sponsor and from the research team at Adelphi Values
  - And of course huge thanks to the patient and parent/caregivers themselves

\* Those authors marked with an \* no longer work for Ironwood or Adelphi Values, but did so at the time of the study



# Key challenges associated with developing pediatric COAs

- **Cognitive, linguistic, physical** and **behavioural** development impact ability to complete PRO measures and engage with interviews
  - Ability to **recall** and **report** on symptoms
  - Ability to complete a PRO measure
- As children develop capabilities are constantly changing
  - Changes can be **non-linear**, boundaries are **‘fuzzy’** especially in some disease areas
- Instrument development must occur within narrow developmental age ranges
- If **multiple** instruments are required, this has implications for analysis and **pooling** of data



# FDA PRO Guidance: Pediatric COAs cannot be treated the same as adult assessments

“It is important that PRO instruments developed for adults are **not** used in pediatric populations **unless** the measurement properties are similar in all groups tested”

“Additional review issues include age related **vocabulary**, language **comprehension**, comprehension of the health concept measured and **duration of recall**”

“Instrument development and validation testing within **fairly narrow age groupings** is important...to determine the lower age limit at which children can **understand** the questions and provide valid and reliable responses”

Read and circle a number.	Strongly Disagree → Strongly Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	



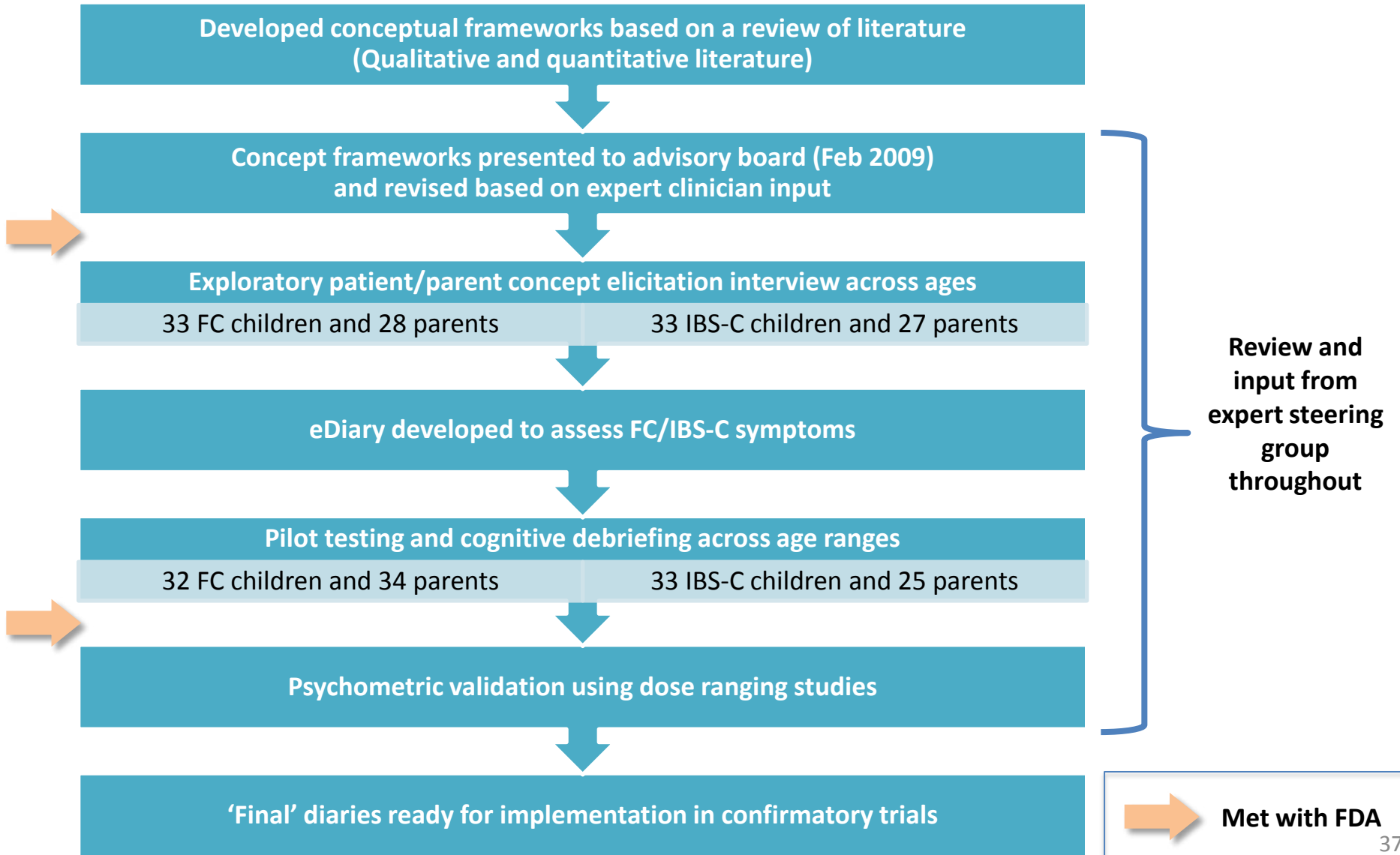
# Pediatric functional constipation (FC) and irritable bowel syndrome with constipation (IBS-C)

- Pediatric FC and IBS-C are chronic gastrointestinal disorders characterised by infrequent bowel movements and abdominal symptoms.
- Rome III diagnostic criteria differ between FC and IBS-C in children and adolescents (4-18 years old), but for both, key symptoms to assess include:
  - Frequency of bowel movements
  - Stool form/consistency
  - Abdominal pain severity
- Assessed through directly asking the patient
- Otherwise, a parent/caregiver must be asked to rate associated observable behaviors

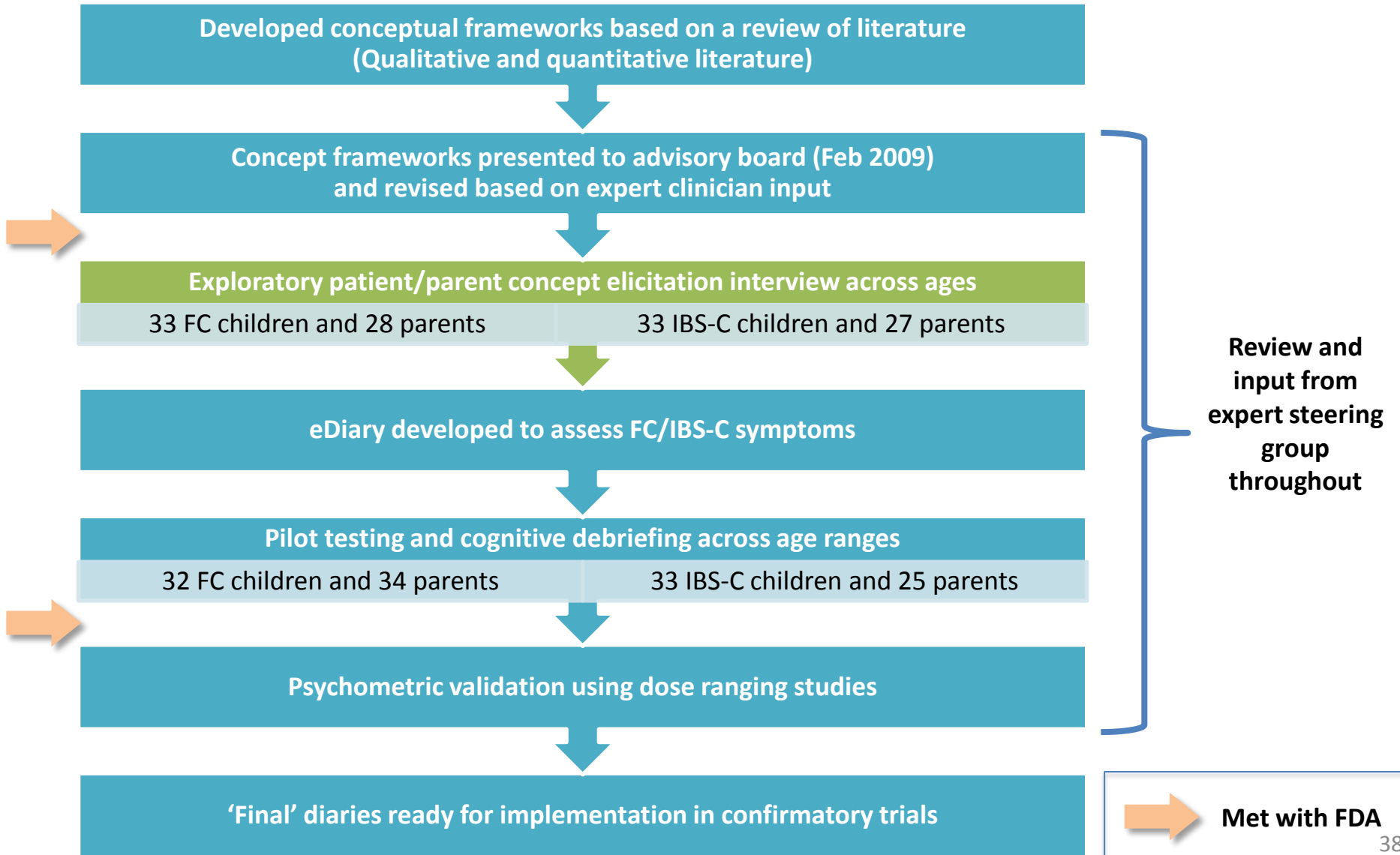
# Considerations prior to designing research

- For trials spanning ages 6-17 years: must decide between 1 or multiple instrument versions
- For children aged 6-9 years old, the **optimal reporter** must be determined:
  - Some children may lack the linguistic, reading, or cognitive ability to provide a valid and reliable self-report.
  - Parents/caregivers of this age range don't typically observe the child's bowel movements closely enough to provide a valid report.

# Ensuring a comprehensive development process



# Ensuring a comprehensive development process



# Tailoring qualitative methods for interviewing across the age range

- **Concept elicitation:** Open-ended, qualitative interviews with children and parents to identify and understand symptoms from patient perspective
- Methods tailored to fit with the age of the child and their ability to report
  - Questions started very open (*“Tell me about a good week with your pooping problems? Now tell me about a bad week”*)
  - Used play-doh, drawing task, toys, child BSFS to elicit content from children
  - Specific probes for symptoms identified in literature review, if not mentioned spontaneously (needed for children who are not always forthcoming)
- **Qualitative analysis** of verbatim transcripts using grounded theory methods and Atlas ti. software, grouping quotes by symptom/concept.

# Concept elicitation sample

- **Study sample:** Children/adolescents with FC and IBS-C and their primary caregivers in the US.
- **Quotas** used to ensure diversity in **age, gender, and severity**.

	Functional Constipation			IBS-C		
Age group	Children/ Adolescents	Primary caregivers	Total	Children/ Adolescents	Primary caregivers	Total
6-8 years	12	12	24	10	10	20
9-11 years	11	11	22	14	12	26
12-17 years	10	5	15	9	5	14
Total	33	28	61	33	27	60



# Creative methods to elicit content from children

- **Toys:** Gender appropriate toys to help younger children talk about their symptoms.



- **Creative activities:** Play-doh® and drawing their symptom experiences helped children to describe and discuss symptoms and related impacts.



*"Yeah, it just feels like something's just stuck, like I have like a rock" (male age 10)*

*"I drew me, like me on the toilet. And I feel sometimes I might cry. And like my stomach, it feels like it's almost like howling, it's going RRRR" (female age 12)*

*"Sometimes, it's just like little balls, I guess you could say. (laughter) Like half of that, and then rolled up" (female age 16)*

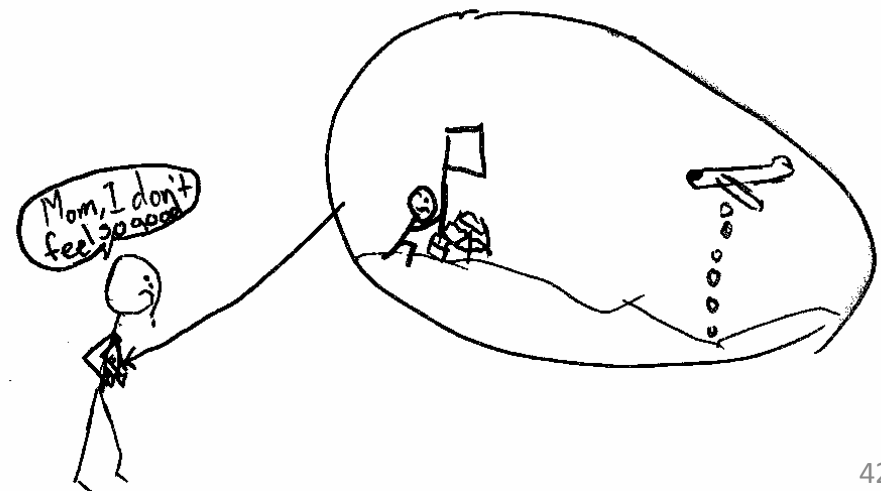


# Example key symptom (Abdominal pain)

- **Abdominal pain:** 30/33 children/adolescents reported experiencing abdominal pain, often reported to be frequent and long lasting.
  - Timing: Commonly reported to occur before bowel movements (BMs) (28/33). 5 children specifically stated that the pain was relieved by defecation.
- The focus of many of the children/adolescents' drawings was on abdominal pain and the associated impact.

*"It just feels like somebody hitting me in my stomach to the point where I have to lay down, or I just have to rest for a while." (female age 14)*

*"Most of the time, my stomach feels like there's kind of a small war, in there, and it feels bad. Like I can feel the pain a lot." (male age 10)*



# Concept elicitation results and conclusions

- Some of the children under 9 showed difficulty in recall or understanding some questions and gave responses that suggested they would have difficulty with recall periods over 24 hours:
  - **Q: “All right. OK, well, do you remember what it was like while you were sitting on the toilet?”** “I can’t really explain it....” (female, age 8)
  - **Q: “What’s the longest time you went without pooping?”** “I went pee.” (male, age 6)

# Ensuring a comprehensive development process

Developed conceptual frameworks based on a review of literature  
(Qualitative and quantitative literature)

Concept frameworks presented to advisory board (Feb 2009)  
and revised based on expert clinician input

Exploratory patient/parent concept elicitation interview across ages

33 FC children and 28 parents

33 IBS-C children and 27 parents

eDiary developed to assess FC/IBS-C symptoms

Pilot testing and cognitive debriefing across age ranges

32 FC children and 34 parents

33 IBS-C children and 25 parents

Psychometric validation using dose ranging studies

'Final' diaries ready for implementation in confirmatory trials

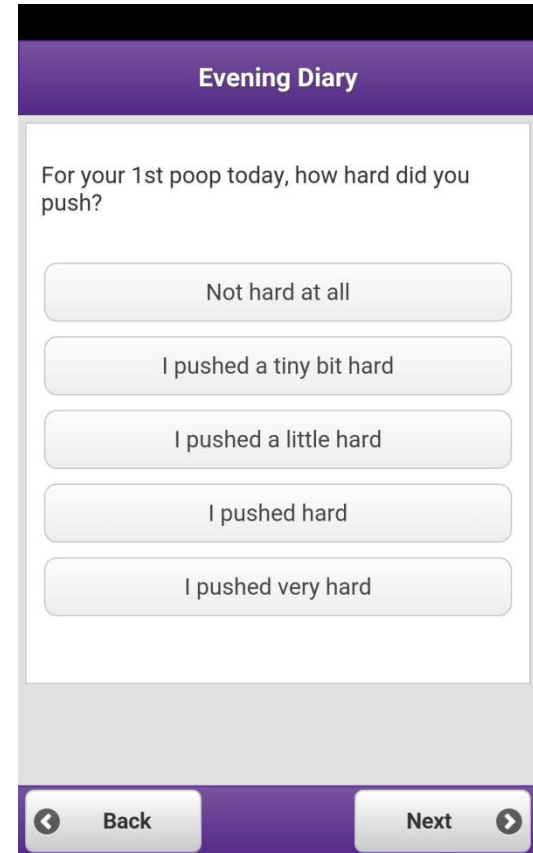
Review and  
input from  
expert steering  
group  
throughout

Met with FDA

# Development of the draft diary

- Conclusions from concept elicitation findings:
  - Symptoms experienced and descriptions **consistent across 6-17 age range** (older children just provided more detail)
- Developed a single PRO to cover both conditions for use across the 6-17 age range
  - daily diary, completed once daily in the evening
  - 24 hour recall period
  - electronic mode of administration (ePRO)
  - Skip pattern/branching logic to reduce respondent burden

- Private
- Fun and engaging for children
- Facilitated clear and simple presentation of content
- Helped to reduce respondent burden through use of skip-patterns/branching logic



The screenshot shows a mobile application interface for an 'Evening Diary'. The title 'Evening Diary' is at the top in a purple header. Below the header, the question 'For your 1st poop today, how hard did you push?' is displayed. There are five response buttons: 'Not hard at all', 'I pushed a tiny bit hard', 'I pushed a little hard', 'I pushed hard', and 'I pushed very hard'. At the bottom, there are 'Back' and 'Next' navigation buttons with arrows.

# Example item on ePRO diary

Evening Diary

Use the card provided to choose the poop that is most like the poop you had today.


- ☐ Type 1
- ☐ Type 2
- ☐ Type 3
- ☐ Type 4
- ☐ Type 5
- ☐ Type 6
- ☐ Type 7
- ☐ I don't know

Back Next

Evening Diary

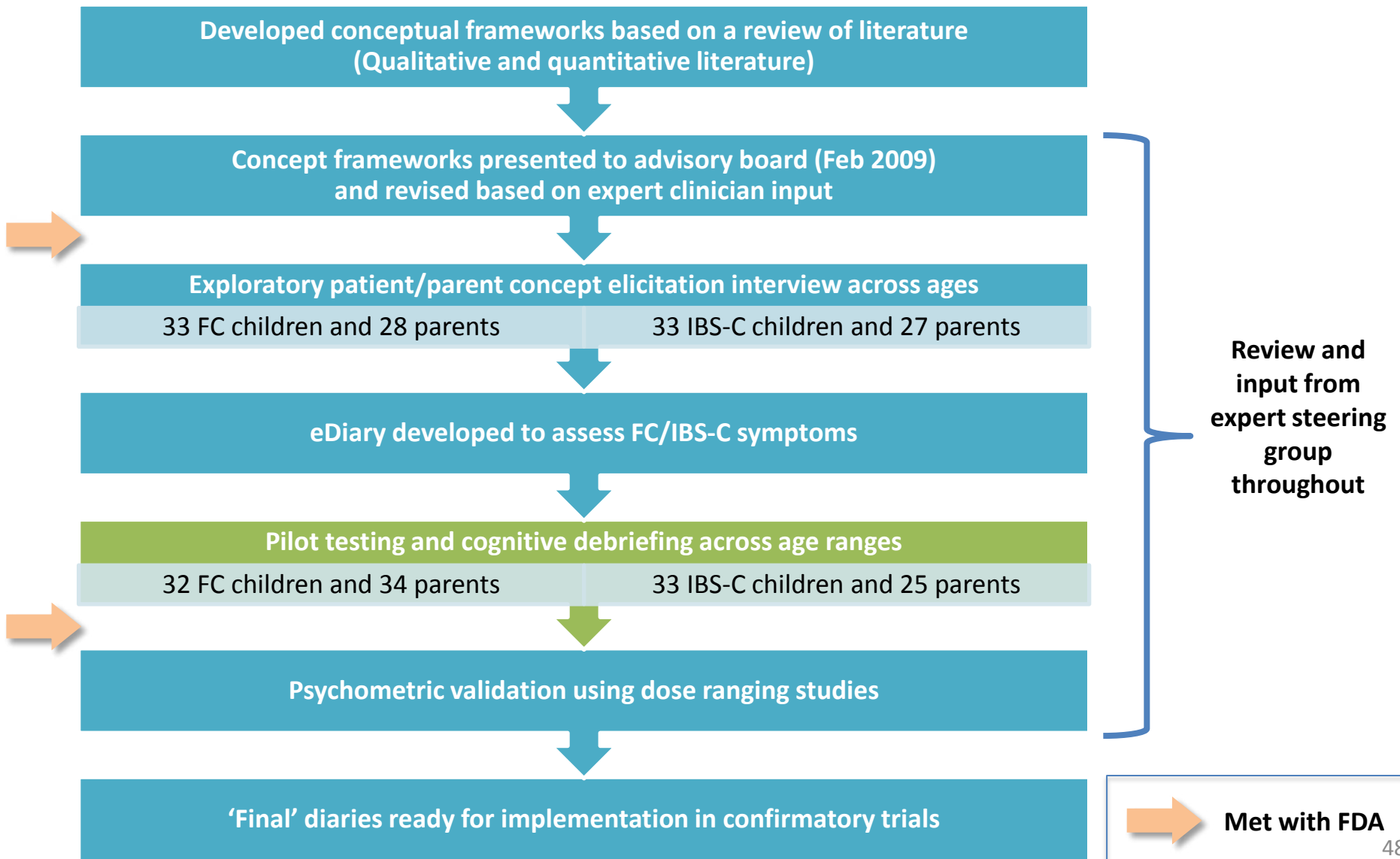
Use the card provided to choose the poop that is most like the poop you had after your clinic visit today.

**Type 2**  
Looks like a fat sausage shape but lumpy and hard



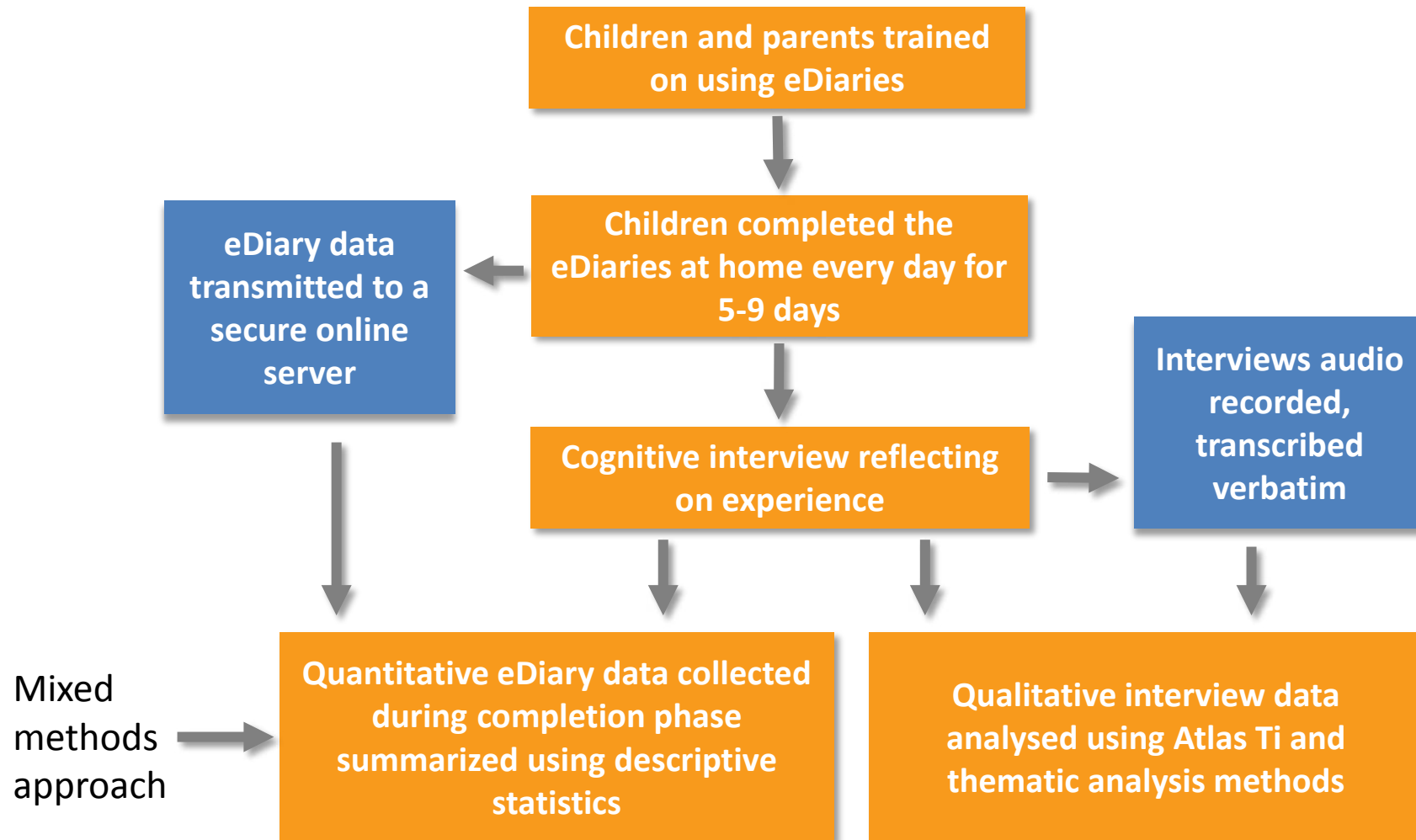
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# Ensuring a comprehensive development process





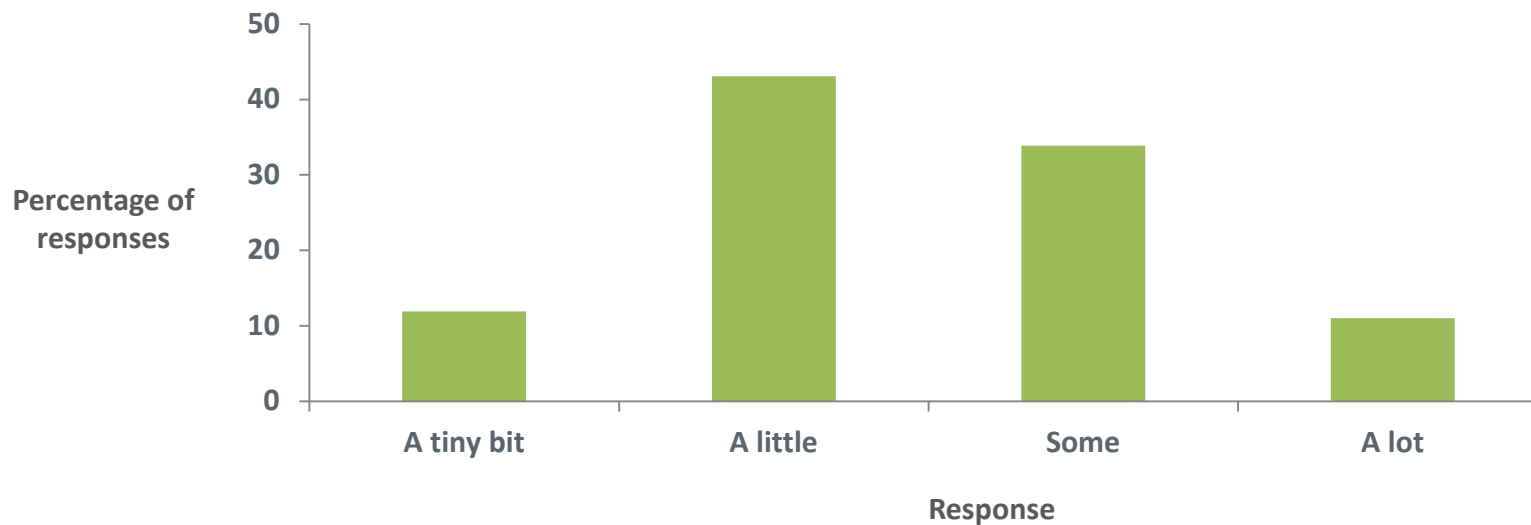
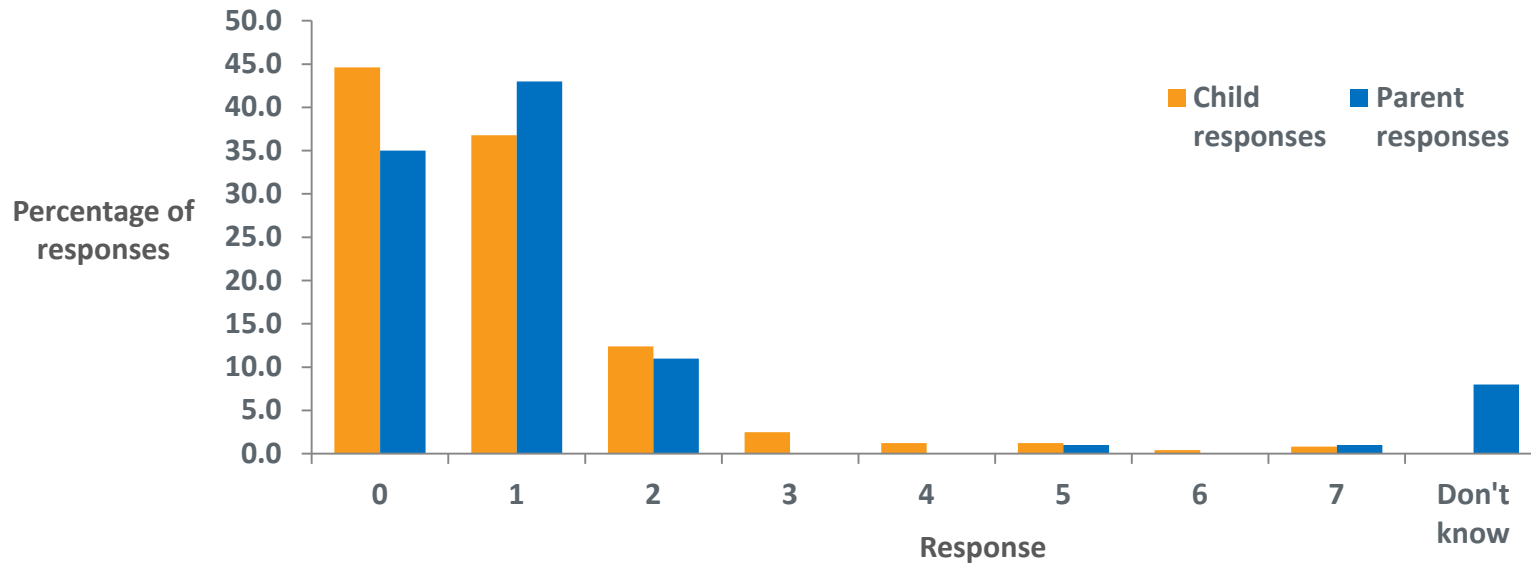
# Pilot testing prior to cognitive interviewing



# Cognitive debriefing results

- Majority of diary items performed well
  - Well understood by all, although 6-8 year olds had more difficulty
  - Interpreted consistently
  - Considered relevant
- Changes to diary:
  - Added an instruction screen to help remind of recall period
  - **Minor** but **important** changes to **14** items
    - e.g. “When you pooped, did your bottom hurt?” (round 1)
    - “When you pooped, did it hurt in your bottom?” (round 2)
- Qualitative findings supported by response distributions from pilot testing data

# Collection of pilot data prior to cognitive debriefing



# Children found ePRO fun and engaging

*"It was touch screen and it worked really easy. Um, like it responded really quickly, didn't take that long."*

*( 11 year old girl)*



*"Well, it was pretty much fun because it's just like this, a DS."*  
*(8 year old boy)*

*"I thought it was simple and didn't—  
wasn't a challenge and it didn't  
interfere with our day or anything"*  
*(Parent of an 11 year old boy)*

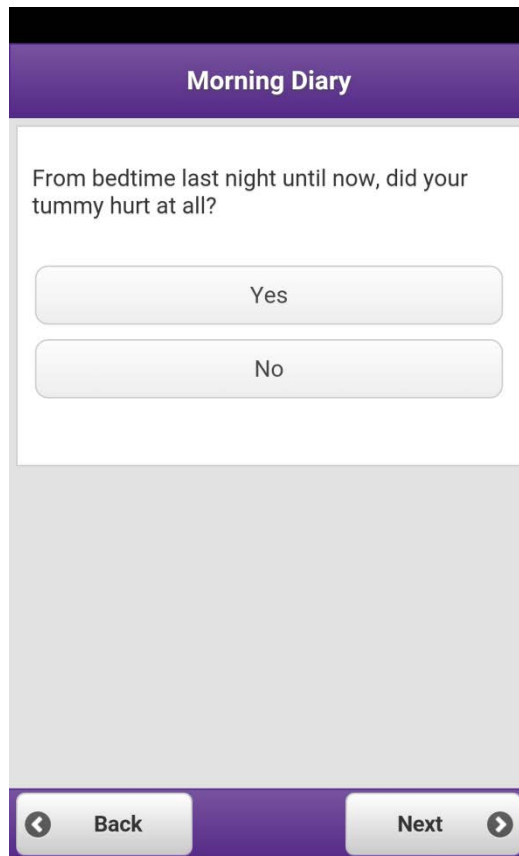


# Cognitive debriefing results

- In rounds 1 and 2, **17/36** children made comments which suggested they may not be fully understanding the 24-hour recall period '**from bedtime last night until now**'
  - **7/17** seemed to only be thinking of the **daytime**
  - **4/17** focused on when they were **in bed** last night
  - **6/17** said they didn't know, or gave **inconsistent** answers
- **16/36** children also had difficulty remembering over 24 hours
- Recall period split into two 12 hour periods and revised items taken into 3rd round of testing

# Shortened recall period

Wording in morning  
items for recall of  
previous night



**Morning Diary**

From bedtime last night until now, did your tummy hurt at all?

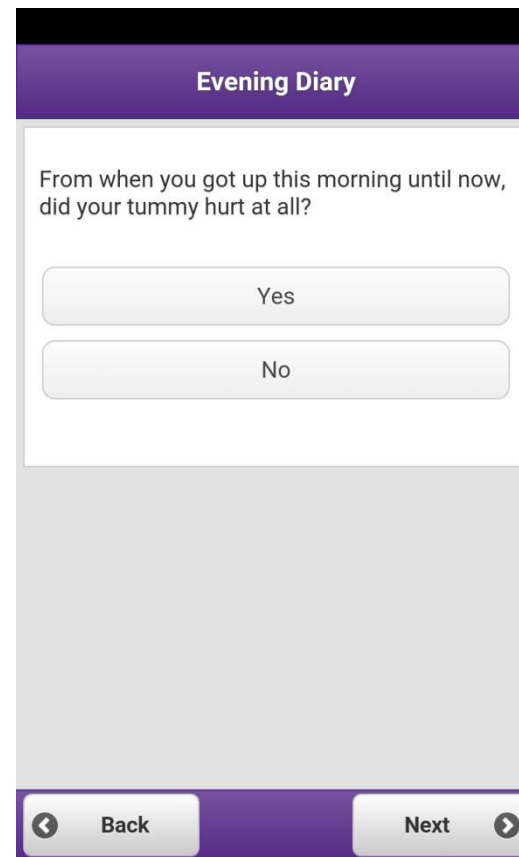
Yes

No

Back Next

The image shows a mobile app interface for a 'Morning Diary'. It has a purple header with the title 'Morning Diary'. Below the header, there is a question: 'From bedtime last night until now, did your tummy hurt at all?'. There are two buttons, 'Yes' and 'No', for the user to select. At the bottom, there are 'Back' and 'Next' navigation buttons with arrows.

Wording in evening  
items for recall over that  
day



**Evening Diary**

From when you got up this morning until now, did your tummy hurt at all?

Yes

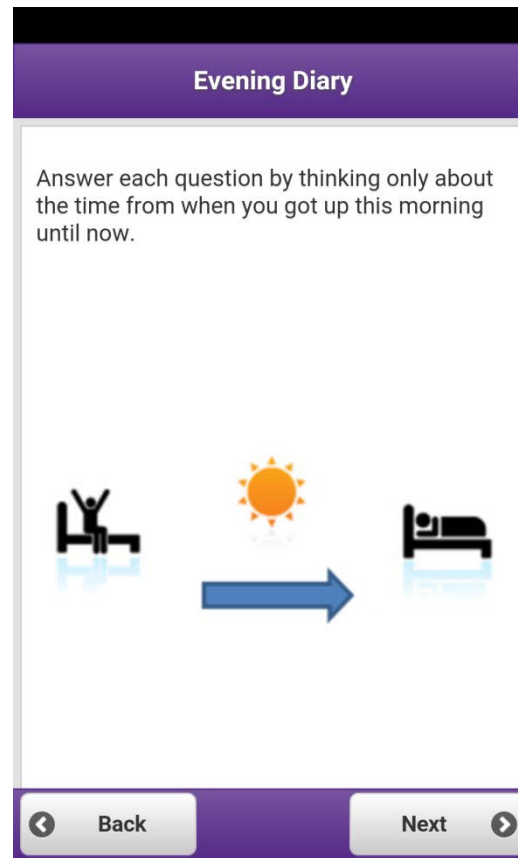
No

Back Next

The image shows a mobile app interface for an 'Evening Diary'. It has a purple header with the title 'Evening Diary'. Below the header, there is a question: 'From when you got up this morning until now, did your tummy hurt at all?'. There are two buttons, 'Yes' and 'No', for the user to select. At the bottom, there are 'Back' and 'Next' navigation buttons with arrows.

# Instructions and image to aid use of correct recall period

- Added an instruction with images to help focus children on the correct recall period



# Improved understanding but concerns remained...



- With 12 hour recall period and addition of the images understanding was much improved.
  - But 4/29 children still had some difficulty with the recall periods.
- Despite extensive testing and refinement, there were some remaining concerns regarding comprehension and use of the recall period in 6-9 year olds especially



# The solution: Interviewer (parent/caregiver) – administered version



- Created the option of the questions being ‘interviewer’ (parent/caregiver)-administered
- Items remain exactly the same, but for those children their parent/caregiver reads the questions out to them verbatim
- The child is still the one who chooses the response
- Parents can help ensure the child understands and remind them of the recall period, but are given strict instructions and detailed training that they should not choose or influence the response

- **Symptoms** and importantly the **words children use** and are able to understand to describe them were **consistent across the age range**
- Wording using **simple language** and **short items** helped ensure comprehension of the items was strong and consistent across the age ranges
  - Supported by item response distributions as part of a **mixed methods** approach
- **Electronic** administration, **visual response scales** also aided comprehension and **minimized burden**

- **Multiple rounds** of rigorous pilot testing and cognitive debriefing identified concerns regarding **ability to read, understand** and use the **recall period** for some of the younger children
- Addressed in part through **shortening** the recall period, use of **images** and **instructions** to focus children on the recall period
- Added an **optional ‘interviewer’ (parent)-administered** version for the 6-11 year old children
- Thus, the **same items** are used **across the range**, but there is **adaptation of administration** method according to age/ability
- Psychometric evaluation will provide further insight into instrument performance

# **Common cold case study: development and use of a pediatric PRO to assess chest congestion symptoms in children, adolescents and adults**

*Rob Arbuckle*

Vice President and UK Managing  
Director, Patient-Centered Outcomes,  
Adelphi Values

- Again, the research presented here was a huge team effort. The following all made substantial contributions to the research at different points:
  - Cathy Gelotte, Patricia Halstead and Brenda Zimmerman from McNeil Consumer Healthcare
  - Tim Shea at Reckitt Benckiser
  - Chris Marshall, Kate Bolton\*, Laura Grant and Kate Burrows from Adelphi Values
  - Antoine Regnault\* from Mapi
  - And of course huge thanks to the patients and parent/caregivers themselves

\* Those authors marked with an \* no longer work for Adelphi Values or Mapi, but did so at the time of the study

# Background to current work

## CHPA

- Adelphi Values initially collaborated with Consumer Healthcare Products Association (CHPA) cold task group members to develop patient reported outcome (PRO) measure items to assess the cold symptoms of **nasal congestion** and **runny nose/sneezing** in children aged 6-11 years.

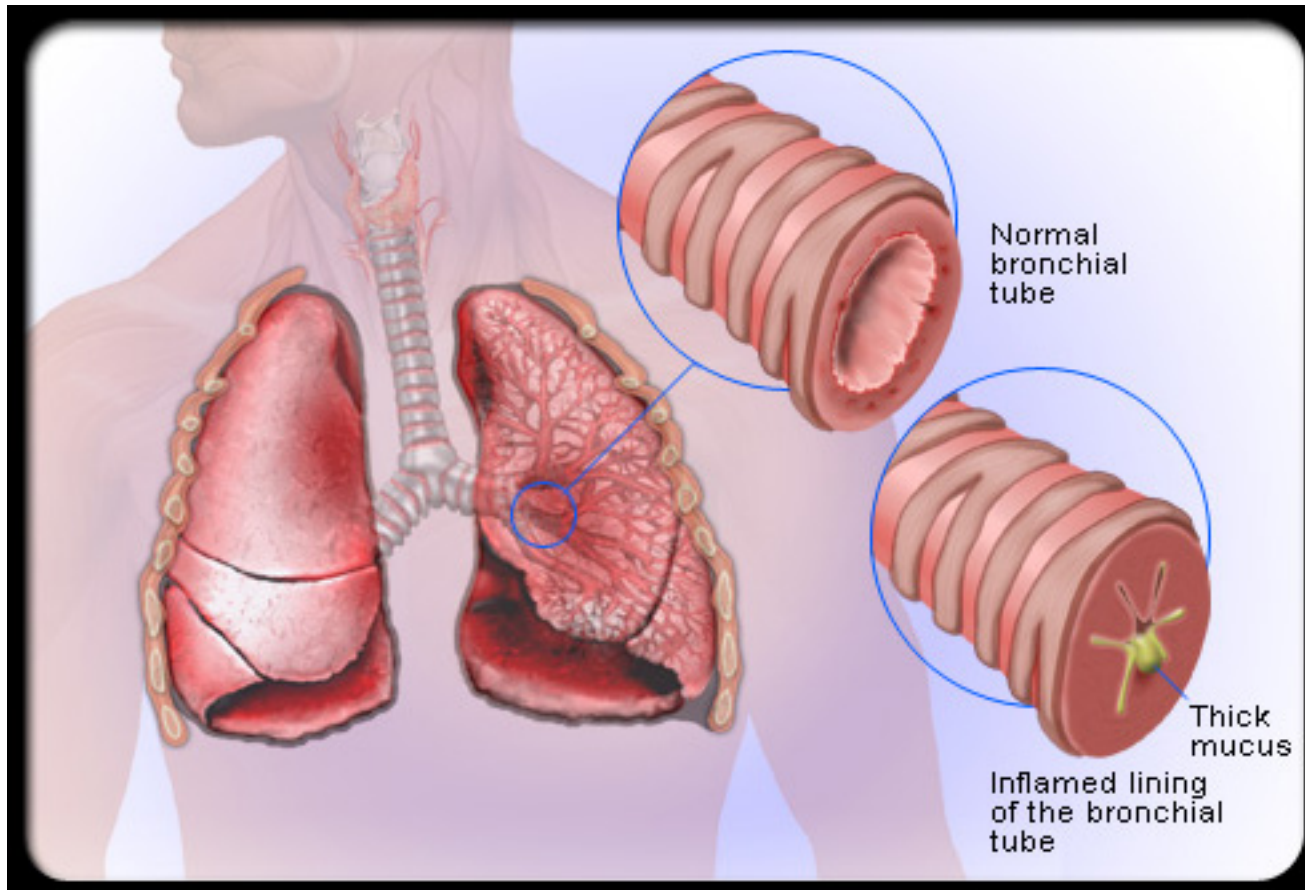
## McNeil

- Building on this original work, McNeil worked with Adelphi Values to develop and psychometrically validate a multiple-symptom PRO instrument (**Child Cold Symptom Questionnaire [CCSQ]**) in paper format that could be used in **children aged 6-11** to support endpoints in pediatric clinical trials to assess the efficacy of multiple-ingredient cold medicines.

## Reckitt Benckiser

- Following the McNeil work, RB were interested in further testing and refining items assessing **chest congestion** to strengthen their value for use in planned studies for chest congestion products.

# Pediatric chest congestion due to a common cold or upper respiratory tract infection (URTI)



# Qualitative and quantitative research to refine a chest congestion PRO

- During the development of the CCSQ the chest congestion items were difficult for children to understand
- Therefore the aim was to conduct further qualitative research to:
  - Further **test/refine** the existing chest congestion items
  - Consider **adding items**
  - Confirm content validity in an ePRO format
  - Confirm whether **adolescents** and **adults** also understood the items as well as **children aged 6-11**





# A 'Sesame Street' approach ... as proposed at this meeting in 2014 by Laura Lee Johnson...



- The CCSQ items were originally developed and validated for use in children **aged 6-11 years**
- But the follow up research aimed to test the refined and expanded set of chest congestion items in children (6-11 years), adolescents (12-17 years) and adults (18+)
- Can the **same instrument** be used across this age range?
- Do adolescents/adults find the items too **simplistic** or **childish**?
- Or are they easy for all to understand?

# Study overview: Objectives and sample

## Study objectives

Explore the qualitative experience of chest congestion

Concept elicitation



Evaluate content validity: relevance and understanding

Cognitive debriefing



Evaluate usability and feasibility of ePRO version

Usability testing



Appropriate to use in children, adolescents and adults

Applicable across ages



## Sample

	Child & adolescent interviews				Parent/Caregiver interviews			Adult interviews		Total Interviews
Age bands (years)	6-8	9-11	12-17	Total	6-8	9-11	Total	18+	Total	
Current cold symptoms	10	10	10	30	10	0	10	10	10	50
Recent cold symptoms	4	3	3	10	0	0	0	0	0	10
<b>TOTAL</b>	<b>14</b>	<b>13</b>	<b>13</b>	<b>40</b>	<b>10</b>	<b>0</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>60</b>

# Conceptual framework (1 of 2)

- Conceptual framework detailing all items and symptom concepts tested
- Deliberately tested multiple similar/redundant items for each concept

***“This morning/This afternoon...”***

ePRO1. “...how hard was it to breathe air deep into your chest?”

Paper1. “...how hard was it to breathe air deep into your chest because of your cold?”

**DIFFICULTY  
BREATHING**

ePRO2. “...how tight did your chest feel because of your cold?”

Paper2. “...how tight did your chest feel?”

**CHEST  
TIGHTNESS**

ePRO3. “...how much has your chest hurt when you’ve coughed?”

Paper3. “...how much has your chest hurt due to being stuffed up?”

**CHEST PAIN**

ePRO4. “...how heavy did your chest feel?”

Paper4. “...how much of the time has your chest felt heavy?”

**CHEST FEELS  
HEAVY**

# Conceptual framework (2 of 2)

*"This morning/This afternoon..."*

ePRO5. "...how much did your chest feel full of mucus (the goo that comes out of your nose)?"

ePRO6. "...how stuffed up did your chest feel?"

Paper5a. "...how much did you feel stuffed up in your chest?"

Paper5b "...how much did you feel clogged up in your chest?"

Paper5c. "...how clogged up did your chest feel?"

ePRO5d. "...how full of stuff did your chest feel?"

Paper6c. "...how clear did your chest feel?"

**CHEST FEELS  
FULL**

ePRO7. "...how hard was it to clear your chest?"

Paper6a. "...how hard was it to clear your throat?"

Paper6b. "...how hard was it to blow your nose?"

ePRO8b. "...how hard was it to cough up mucus (goo ) from your chest?"

**DIFFICULTY  
CLEARING  
MUCUS**

ePRO8. "...how much did you wheeze (make a noise) when you breathed?"

Paper7a. "...how much did your chest make a rattling noise when you breathed?"

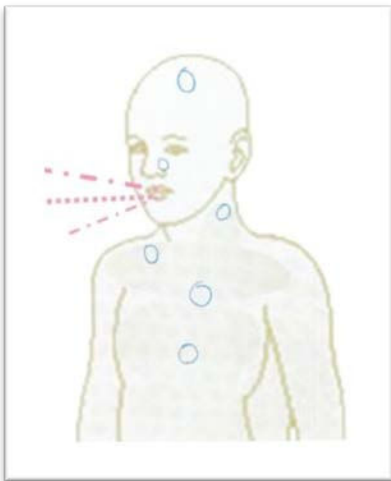
Paper7b. "...how much have you noticed a sharp noise when you breathed in or out?"

**NOISE WHEN  
BREATHING**

- **Creative methods:** During the qualitative interviews, several activities were used in support of *open-ended questioning* to help elicit relevant content from children:
  - **Circle parts of the body:** Presented with an outline of a human body and asked to mark on it *and talk about* areas of their body affected.
  - **Free-drawing:** Asked to draw “how it feels when you have a cold”, and explain their drawing to the interviewer.
  - **Animal task:** Children were asked to describe their cold as an animal.
  - **Card-sorting task:** Response options provided on cards in a random order, then the child asked to sort into the order they think is appropriate.
  - **Parent-child combined debriefing:** Parents and children brought together to understand how parent-administration would impact response selection.

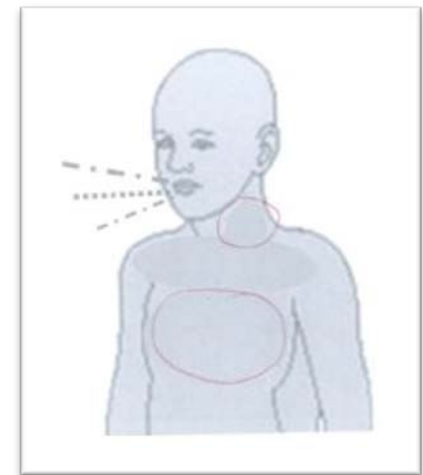
# Results of creative tasks (circle parts of the body)

- Children were asked to mark any areas of their body that felt different during their cold:



**Q: OK. And what parts did you circle there?** "Throat." "Mm-hmm (yes) why that one?" "Because the sore throat. (11 year old boy)

**Q: "OK. And then this other big area down here. What's that area?"** "Um, that's in my chest." "**What - what does that feel like in there?**" "It feels like it's like really like - like very - feels like a lot - like a lot of bad stuff are in there and like a lot of things like bad. Like, um, you feel like you just ate something that you're not supposed to eat." (7 year old girl)



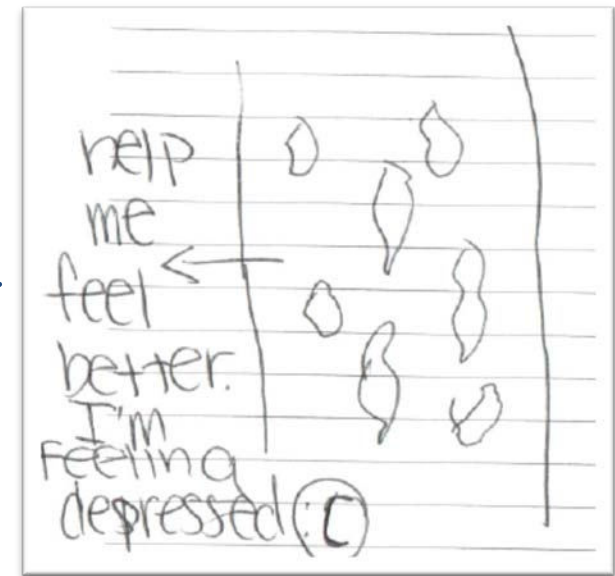
# Results of creative tasks (free-drawing task)

- Children were asked to draw how their chest feels during a cold:



*"That I have a harsh cough, uh, and just harsh through my mouth – m – the cough"*  
(0107-RC-M-8)

*"Germs on my chest and they're all like saying oh, help me, make me feel better. I'm feeling depressed. And, um, they're crying."*  
(0110-CC-F-15)



# Results of creative tasks (animal task)

- Children were asked to describe their cold as an animal:

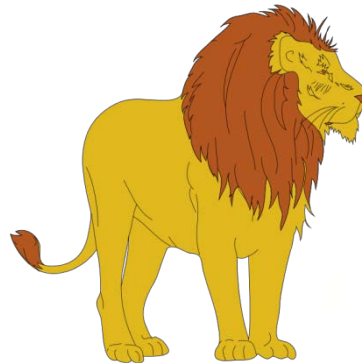


*"It kind of feels like an elephant's on me - it's like hard to breathe and stuff - it just feels like a lot of weight's on me."  
(0114-RC-F-14)*

*"Rabbit - because I can feel it going up and down"  
(0206-CC-M-7)*



*"Like a hamster or something, because those squeak a lot... because the squeaking is kind of like wheezing"  
(0216-CC-F-9)*

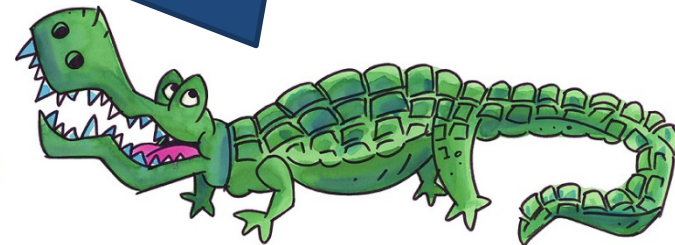


*"A lion - because - it really irritates me when I cough" (0119-CC-M-11)*

*"I think I would choose maybe a snake or an alligator, because you're like - it comes up suddenly, and then it goes away for a little bit, and then it comes up suddenly again." (0102-CC-F-11)*



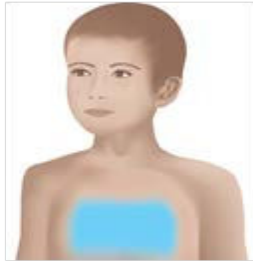
*"A gorilla, because it like beats on its chest and that's how it feels when my chest is like beating."  
(0101-CC-F-8)*





- **Child-friendly PRO items**
  - **Simply worded, short** items that reflected children's **natural language**
  - Each verbal response scale also included a **pictorial scale** beneath.
  - **Illustrations**: Images highlighted the relevant area of the body

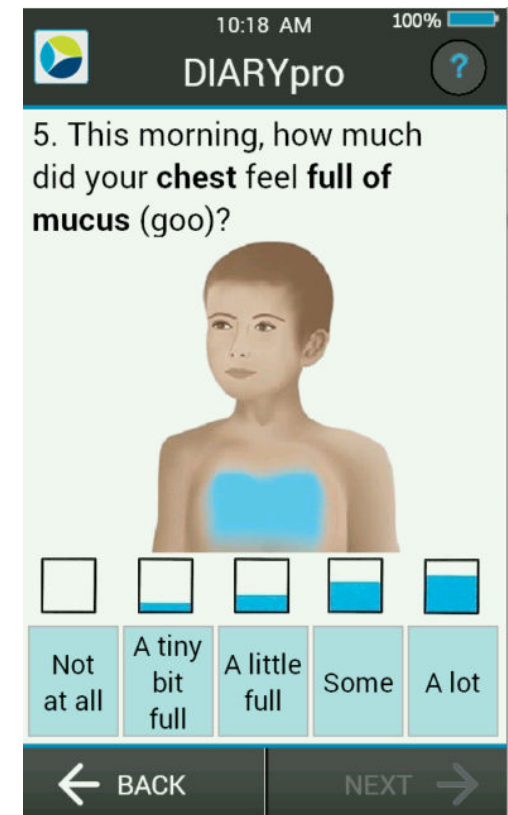
This morning, how hard was it to **breathe air deep** into your **chest** because of your cold?



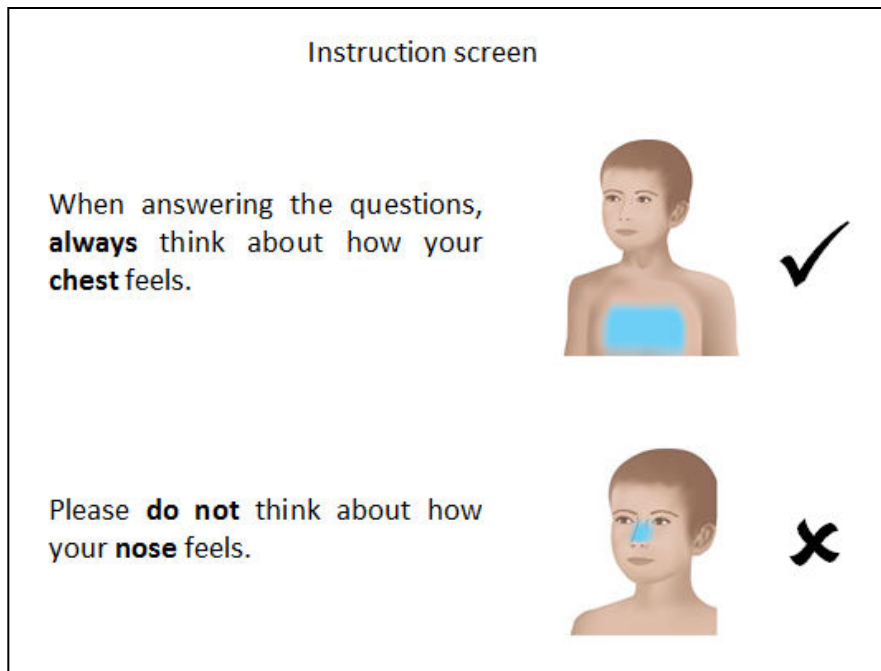
Not hard at all    A tiny bit hard    A little hard    Hard    Very hard

# Development of ePRO version

- Transferring the items from paper to an ePRO platform had several advantages for a pediatric population:
  - Confusion of how to **select an answer** was removed.
  - Children found ePRO more fun
  - **Alarms** were used to encourage children to remember to complete their diary at the correct time
  - Data could be **time stamped**



- An instruction screen was added between rounds to the ePRO to encourage participants to focus on their chest rather than nasal symptoms when answering the questions was debriefed to assess understanding.



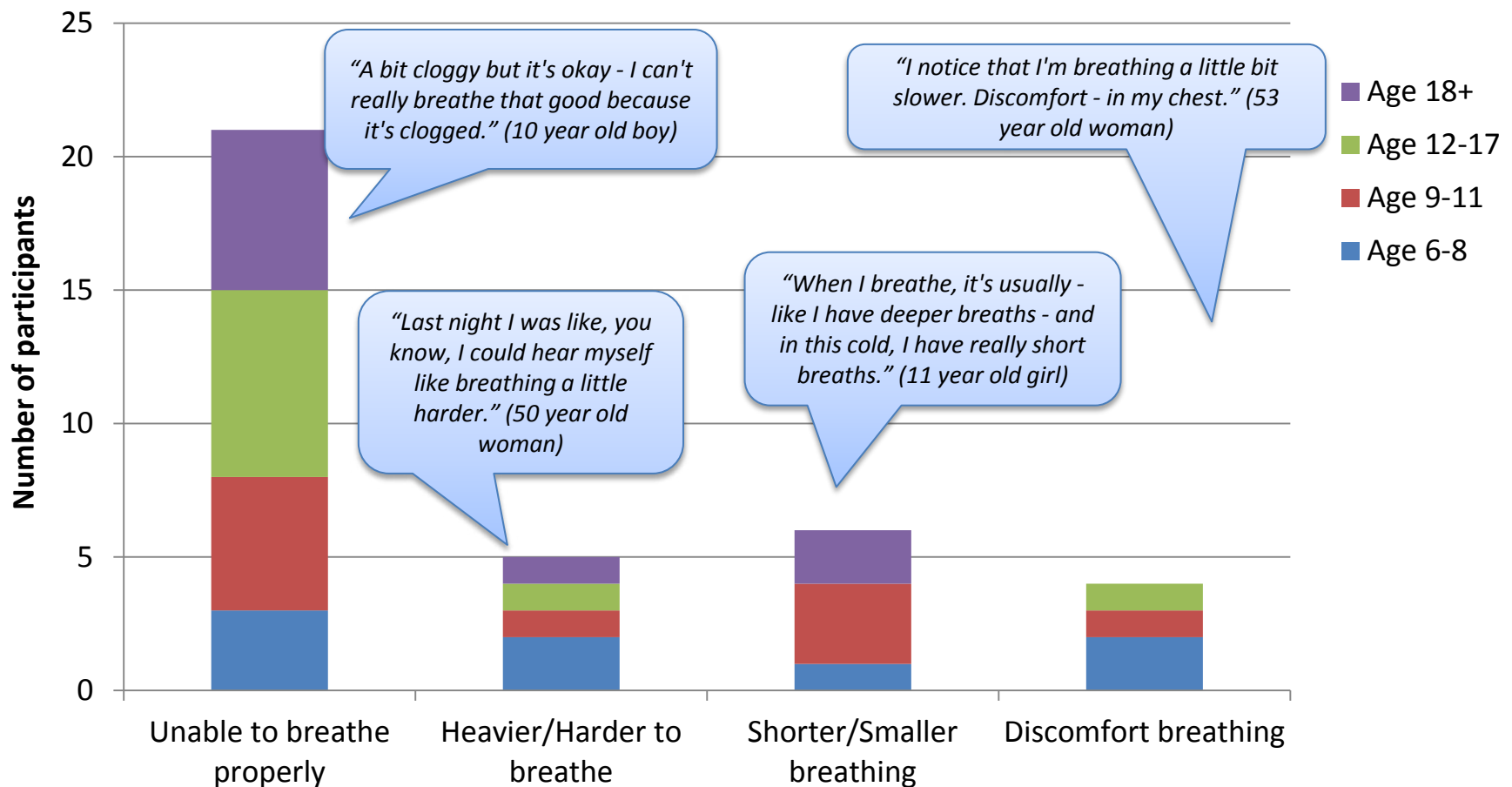
**21 out of the 23 participants** asked understood these new instructions

*"Think about your chest area and not your nose, because those are very different things." (11 year old girl)*

*"Uh, that was helpful to include." (12 year old boy)*

# Example concept elicitation results for 'difficulty breathing'

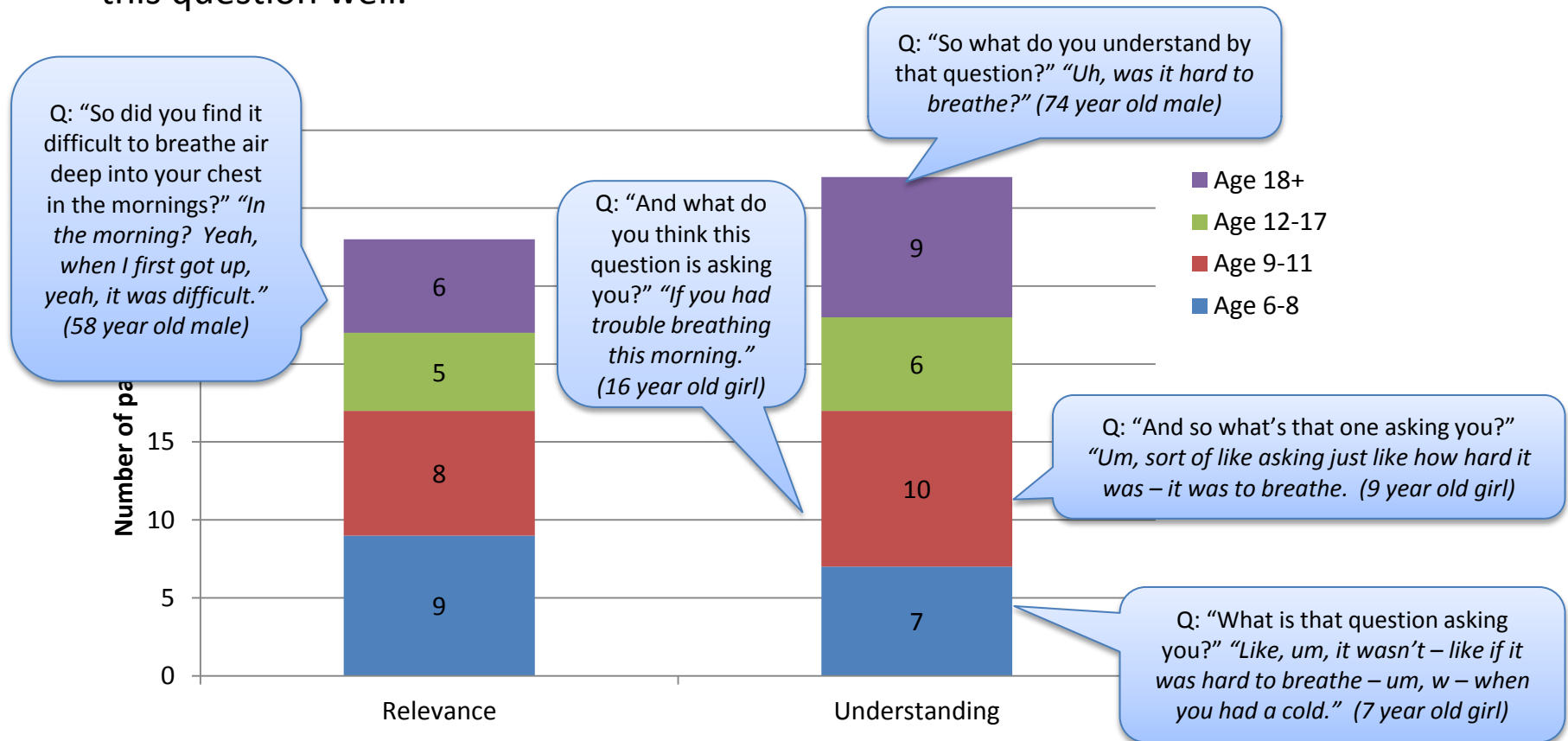
- A total of 37/49 participants reported experiencing difficulty breathing: 16 spontaneously (32.7%) and 21 when probed (42.9%)



# Example cognitive debriefing results for 'difficulty breathing' item

“...how hard was it to **breathe air deep** into your **chest** because of your cold?”

- **Relevance:** 28 out of the 40 participants (70.0%) said that this question related to a symptom they experienced during their cold.
- **Understanding:** 32 out of the 34 participants asked (94.1%) appeared to understand this question well.



# Conceptual framework (1 of 2)

- > Updated conceptual framework: changes in **red**, **bold items** are those chosen to take into the naturalistic study

*“This morning/This afternoon...”*

**ePRO1. “...how hard was it to breathe air deep into your chest?”**

Paper1. “...how hard was it to breathe air deep into your chest because of your cold?”

**DIFFICULTY  
BREATHING**

ePRO2. “...how tight did your chest feel because of your cold?”

**Paper2. “...how tight did your chest feel?”**

**CHEST  
TIGHTNESS**

**ePRO3. “...how much has your chest hurt when you’ve coughed?”**

Paper3. “...how much has your chest hurt due to being stuffed up?”

**CHEST PAIN**

**ePRO4. “...how heavy did your chest feel?”**

Paper4. “...how much of the time has your chest felt heavy?”

**CHEST FEELS  
HEAVY**

# Conceptual framework (2 of 2)

*"This morning/This afternoon..."*

ePRO5. "...how much did your chest feel full of mucus (~~the goo that comes out of your nose~~)?"

ePRO6. "...how stuffed up did your chest feel?"

Paper5a. "...how much did you feel stuffed up in your chest?"

~~Paper~~ePRO5b. "...how much did you feel clogged up in your chest?"

~~Paper~~ePRO5c. "...how clogged up did your chest feel?"

ePRO5d. "...how full of stuff did your chest feel?"

Paper6c. "...how clear did your chest feel?"

CHEST FEELS  
FULL

ePRO7. "...how hard was it to clear your chest?"

Paper6a. "...how hard was it to clear your throat?"

Paper6b. "...how hard was it to blow your nose?"

~~Paper~~ePRO8b. "...how hard was it to cough up mucus (~~gee~~-gunk) from your chest?"

DIFFICULTY  
CLEARING  
MUCUS

ePRO8. "...how much did you wheeze (make a noise) when you breathed?"

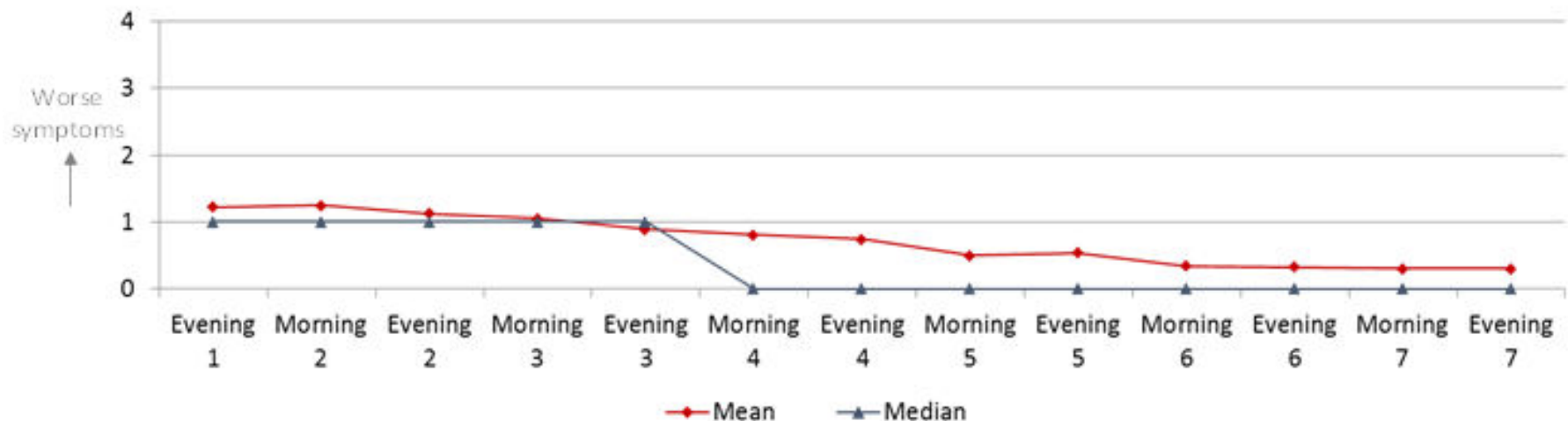
Paper7a. "...how much did your chest make a rattling noise when you breathed?"

Paper7b. "...how much have you noticed a sharp noise when you breathed in or out?"

NOISE WHEN  
BREATHING

# Example psychometric results for 'difficulty breathing'

- The results of the **psychometric evaluation** of the CCSQ provide evidence that the chest congestion items can provide valid and reliable data when used with children aged 6-11 years old.
- The graph below presents the **changes in mean score** for the difficulty breathing single-items across 7 days (n=138).





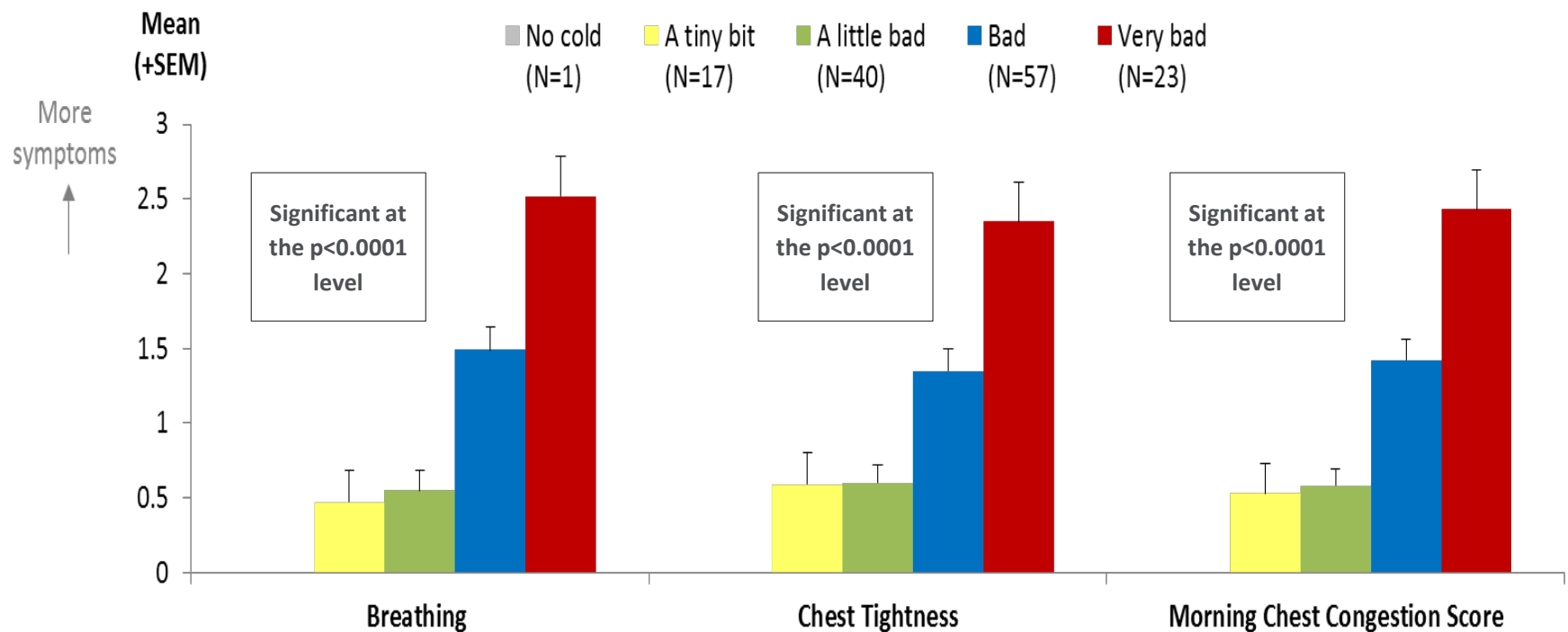
# Test-retest reliability

- Comparison of test-retest reliability between age groups between Day 2 and Day 3 in those children "unchanged or almost the same" on a PGI-C (n=106)

Item	Age group	N	Mean change (SD)	P-value	ICC
Chest tightness	6-8 years	53	-0.06 (1.03)	0.69	0.67
Breathing			-0.13 (0.79)	0.23	0.81
Chest tightness	9-11 years	53	-0.32 (0.80)	0.00	0.72
Breathing			-0.23 (0.70)	0.02	0.78

# Example psychometric results for 'chest tightness'

- The single and multi-item scores were **compared among groups** defined according to ratings of overall cold severity as reported by the children on a child global impression of severity.
- Similar results were again observed within age subgroup (6-8 vs. 9-11).



# Example of team completion aiding comprehension during original CCSQ development



- For the first 45 minutes 10 parents and 6-8 year old children were interviewed separately in parallel.
- In the final 15 minutes they were brought together and observed completing the draft instrument together as a team
- All 10 parents rephrased the wording of at least one question to ensure their child understood.
  - Most were minor changes to use words the child knew: e.g. “how painful” to “how sore”.
  - None of the paraphrasing changed the intended meaning.
- 7 parents questioned their child’s answer at least once.
  - BUT only one six year old (208-RC-F-6-C) actually changed her response.
  - The other six children kept their original answer despite being challenged by their parent.

# Example of team completion aiding comprehension during original CCSQ development

- Several parents reminded their children (aged 6-11) of a specific time they may have experienced a symptom during the day

**DAD:** “When you woke up this morning until now, how has your throat felt?”

**CHILD:** “Mm, not at all sore.”

**DAD:** “In the morning it didn’t?”

**CHILD:** “Mm, actually a tiny bit sore.”

# Example of a parent helping a child to provide more valid answers



- **Dad:** “Does your chest hurt you when you breathe? Does it make you want to cough when you breathe in and out?”
- **Child:** “Not today.”
- **Dad:** “Even when you breathe deep? It’s OK?”
- **Child:** “Yeah, it’s fine.”
- **Dad:** “OK. Even if you - if you run or if you are - if you take deep breaths do you feel like you need to cough?”
- **Child:** “No, not today, but generally when I had the cough yeah. It was bad.”

- How much help from parents explaining items is appropriate?
  - Should parents just be reading verbatim and reminding of the recall period?
  - Or is it OK to reword into language the child understands?
  - Will parents follow instructions to the letter anyway?

# Results and conclusions

- In-depth qualitative research, interrogating relevance and understanding of specific terms, has aided development of **simply worded** items that were **well understood**
- Qualitative findings suggest that the same items are acceptable to use with **children, adolescents** and even **adults**
- Initial psychometric data provided supportive evidence that the items were **valid** and **reliable** across the **6-11 age range**
- Younger children did have more difficulty reading and understanding items
- Screening based on reading ability is one way to handle this
- There is also evidence that **parent support** can help ensure the younger children understood the items correctly
- But need **clear training** regarding the level of help is appropriate for parents to give

# **eCOA in Pediatric Clinical Trials: Case Studies**

*Valdo Arnera, MD*

Scientific Advisor and General  
Manager ERT Geneva, ERT



# eCOA Yields Fewer Errors

A randomized trial of electronic versus paper pain diaries in children:  
impact on compliance, accuracy, and acceptability

Tonya M. Palermo<sup>a,\*</sup>, Duaré Valenzuela<sup>a</sup>, Paul P. Stork<sup>b</sup>

## Study Design

- 60 children with headaches or JIA (ages 8-16) randomized to complete either e-diaries (handheld) or paper diaries at home daily for 7 consecutive days
- Monetary incentives (\$10) used to encourage compliance **in both groups**

## Results

- 83.3% of children with e-diaries and 46.7% of children with paper diaries were 100% compliant
- Paper diaries contained significantly more errors and omissions than e-diaries ( $P < 0.001$ )
- Both formats rated as highly acceptable and easy to use

# eCOA Yields Improved Statistical Power

Merck	Novartis
<p><b>Insomnia: Standard Care</b></p> <ul style="list-style-type: none"><li>• 35% lower standard deviation on the LogPad</li><li>• Study power with 56% fewer subjects</li></ul>	<p><b>Constipation in Men</b></p> <ul style="list-style-type: none"><li>• Phase III Trial called for 1,026 subjects</li><li>• Market approval coincidentally granted after 322 subjects</li><li>• Efficacy was proven with 69% fewer patients</li></ul>
<p>ISOQOL 2004 “Stating the Art: Advancing Outcomes Research Methodology and Clinical Applications” S Raymond, J Pearson</p>	<p>Johanson et al., poster presented at World Congress of Gastroenterology 2005</p>

# eCOA Yields More Accurate Data



## Study Design:

- Type 1 diabetes subjects (n=37) aged 7-18 years
- All completed paper diary for two weeks, then randomized to either mobile phone or computer (two weeks) to record number of hypoglycemia events

## Results:

- 65% (24/37) reported hypoglycemia on paper
- 95% (18/19) reported hypoglycemia on mobile phone
- 89% (16/18) reported hypoglycemia on computer
- Using technology, frequency of hypoglycemia was >3 times than previously recognized, and similar to that reported with CGM<sup>1</sup>

# eCOA Yields Higher Reliability

*Journal of Asthma*, 2012; 49(9): 952–960

## **An Electronic Diary Is Shown to Be More Reliable than a Paper Diary: Results from a Randomized Crossover Study in Patients with Persistent Asthma**

ANDREA M. IRELAND, PH.D., M.P.H.,<sup>1</sup> INGELA WIKLUND, PH.D.,<sup>2,\*</sup> RAY HSIEH, M.S.,<sup>1</sup> PETER DALE, M.Sc.,<sup>3</sup>  
AND ERIN O'ROURKE, B.S.<sup>1</sup>

### Study Design:

- Asthma patients (n=47) equivalence study (e-diary with integrated PEF meter vs paper) Adolescents and adults completed diaries for 14 d twice daily
- Diary: asthma symptoms [Output: symptom free days (SFD)] rescue medication [Output: rescue free days (RFD)]

### Results:

- Test-Retest: Patients categorized as having minimal changes in asthma symptoms (PGIC) had SFD's with similar intraclass correlation coefficients (ICC) for e-diary (0.75) vs paper (0.77) and for RF similar but lower ICC for e-diary (0.63) vs paper (0.60)
- Patients categorized as having  $< \pm 15\%$  change in FEV1 had SFD's with similar ICC for e-diary (0.71) vs paper (0.74) and for RFD good ICC for e-diary (0.78), but not paper (0.67)

### Conclusions:

- Test-retest reliability of SFD's for e-diary and paper met or exceeded acceptable thresholds in all 3 patient categories One category wherein, the RFD met criteria for e-diary, but not paper diary
- Timely data entry improved data quality.

# eCOA Yields Higher Levels of Compliance

## Study Design

- Patients (n=93, age=8-16), with recurrent headaches, juvenile chronic arthritis or sickle cell disease completed:
  - In-clinic retrospective questionnaires (last 4 weeks)
    - Children's Activity Limitation Interview (CALI)- 8 most limited activities on a 5-point scale
    - FACES Pain Scale
    - Revised Child Anxiety Depression Scale
  - At home over the next 7 days a daily evening diary on paper (n=65) or electronically (n=28) - eDiary had build-in response loop and audible alarms
    - Daily pain intensity, location of pain, daily activity limitations

## Results

- Compliance was higher with eDiary (6.9 days completed, on average) than with paper (5 days)
- Young children (aged 8-12) completed more diary days than adolescents (aged 13-16) ( $p<0.0.5$ )

# eCOA Led to Improved Health Outcomes

## Study Design

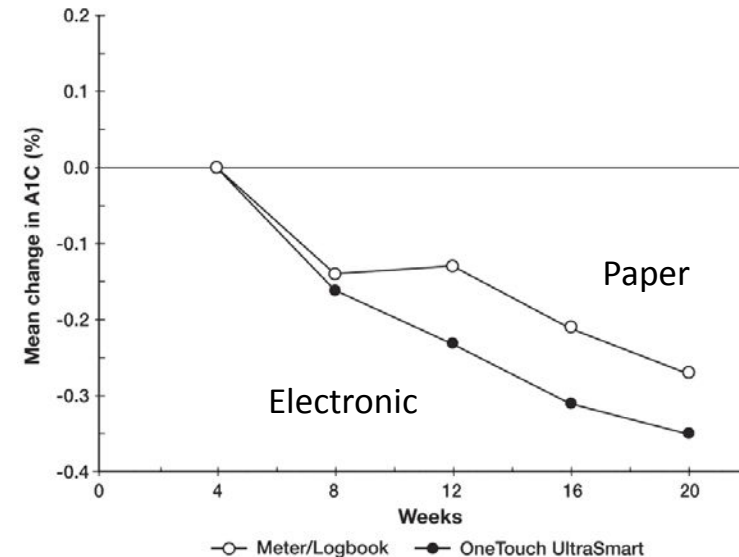
- Adult and pediatric (n = 205) insulin-treated type 1 and 2 diabetics, randomized for 16 wk study
- Electronic group: glucometer integrated to electronic diary (n=113)
- Paper group: glucometer and paper diary (n=92)

## Results

- Both paper and electronic groups had a decrease in HbA1c levels during the trial
- Electronic group had a significantly greater ( $P = 0.022$ ) decrease than paper

## Conclusions

- Use of a glucometer integrated to an electronic diary had greater improvement in HbA1c levels than paper and may be due to increased monitoring causing positive behavioral changes



# Gamification Increases Treatment Adherence (1/2)

## A Video Game Improves Behavioral Outcomes in Adolescents and Young Adults With Cancer: A Randomized Trial

### Study Design

- Cancer patients (13-29 years (N=375)) randomized to receive mini-computer with commercial game alone (control) or commercial game plus Re-Mission, a role-playing video game where users control nanorobot within cancer patient's body (intervention).
- Assessed at baseline, 1 month and 3 months post-intervention
- Goal: Education of various treatments: why they are needed and what they do
- Primary Endpoint: Adherence to antibiotics measured by medication event monitoring system (MEMS)-cap; Adherence to oral chemotherapy measured by HPLC of patient's blood

# Gamification Increases Treatment Adherence (2/2)

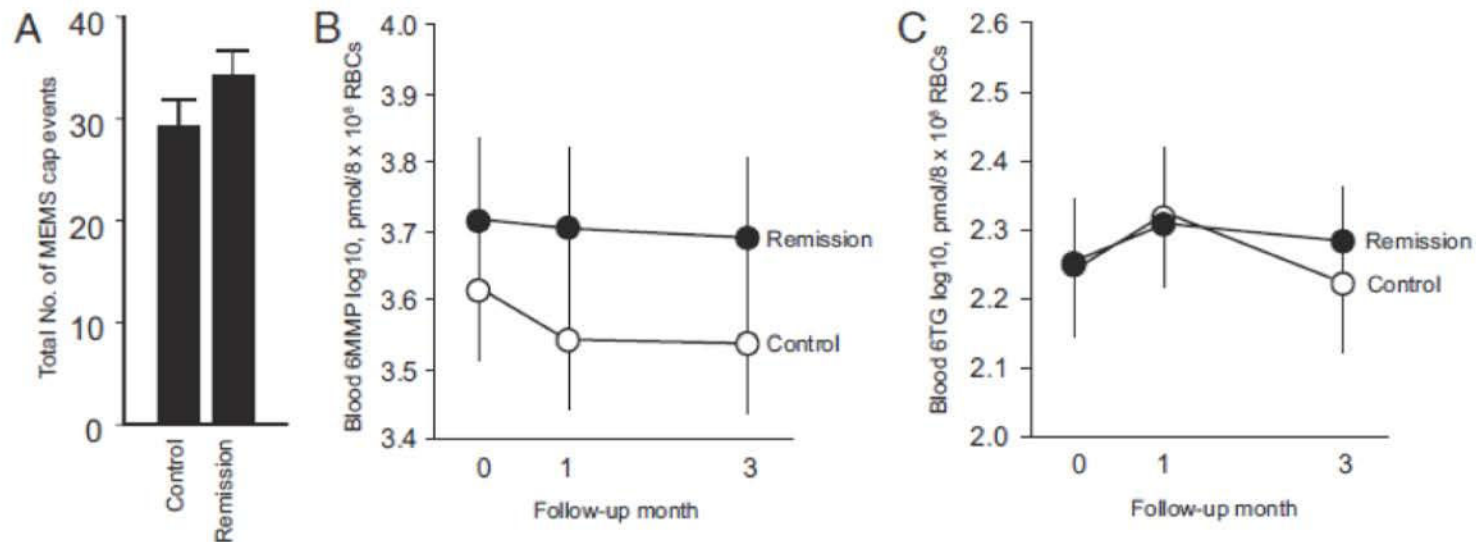


FIGURE 2

Oral medication prescription adherence as measured by frequency (transformed) of TMP/SMX vial cap openings (MEMS) (A) and red cell 6MMP (B) and 6-TG (C) levels according to study group.

## Results

- Self-reported treatment adherence did not differ, but adherence measured by Medication Event Monitoring System (MEMS)-cap showed a 16% increase in intervention group; Adherence to 6MMP significantly higher in intervention group.
- Cancer-related knowledge and cancer-specific self-efficacy increased significantly in intervention group; no difference in QoL



# Gamification Yields Greater User Engagement Among Pediatric Patients<sup>1</sup>

- Gamification strategies:
  - Narrative, storytelling
  - Feedback
  - Rewards for accomplishing tasks
    - points, status, filling a progress bar
  - Competition and/or teamwork
- Gamification could improve:
  - User engagement, motivation, compliance
  - Data quality
  - Learning
  - Empowerment/Investment in one's own health



# eCOA Yields High Acceptability Among Pediatric Patients



## **Brief Report: Assessment of Children's Gastrointestinal Symptoms for Clinical Trials**

*Lynn S. Walker,<sup>1</sup> PhD, and Susan C. Sorrells,<sup>2</sup> PharmD*

*<sup>1</sup>Vanderbilt University School of Medicine and <sup>2</sup>GlaxoSmithKline, Inc.*

### Study Design

- Pilot study examined electronic data collection (using PDAs) of irritable bowel syndrome symptoms in a pediatric population (6-10 years). Subjects (n=11) worked with parents to complete daily diaries for one week.

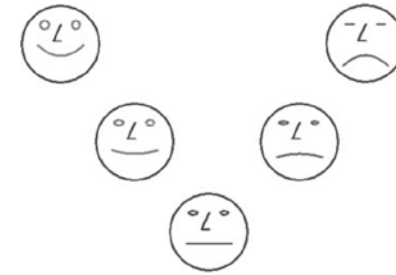
### Results

- Subjects were 100% compliant
- Parents reported that PDAs were enjoyable and easy to use. Parents and children expressed willingness to participate in a similar study in the future

### Conclusion

- Electronic data collection can benefit studies requiring subjective reports of symptoms, elevating compliance and children's willingness to participate

# Faces Scales as eCOA Yields High Acceptability Among Pediatric Patients



## Study Design:

- Children aged 3-17 years old
- Pediatric inpatients (n=54) tested Computer Face Scale and paper Wong-Baker Face Scale.
- Computer Face Scale: Child adjusts shape of cartoon face (smiling/frowning)
- Non-hospitalized children (n=30) completed Computer Face Scale only.

## Results:

- Computer Face Scale had acceptable psychometric properties and correlated with Wong-Baker Face Scale (0.72)
- Computer Face Scale was preferred by most children (76%)

# eCOA Yields High Acceptability Among Health Professionals



## Study Design

- 15 pediatric rheumatologists (67% practicing over 10 years) were surveyed about electronic (handhelds) and paper versions of pediatric pain questionnaires

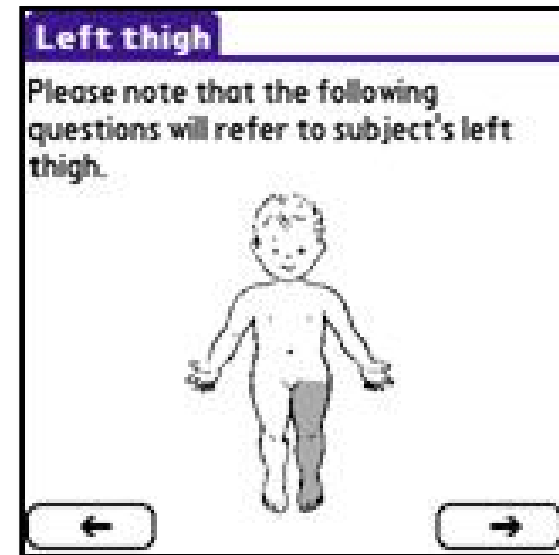
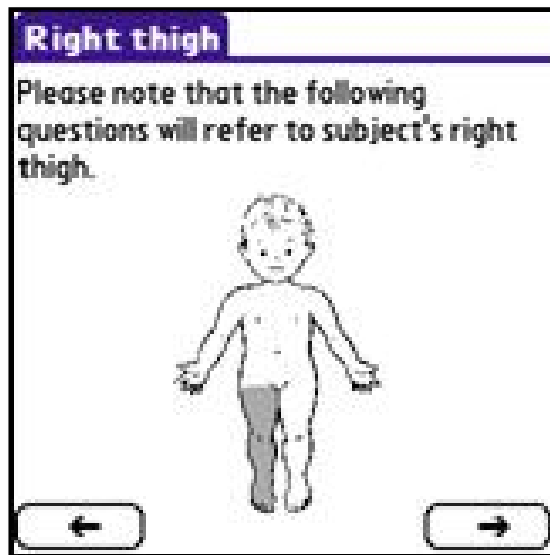
## Results

- 67% of rheumatologists found the electronic (handheld) mode to be more time efficient than paper and preferred the electronic reports
- 60% of rheumatologists would recommend ePRO to colleagues

## Conclusion

- Pediatric rheumatologists preferred electronic pain assessments over paper

# eCOA Best Practice: Use of Body Diagrams





# eCOA Best Practice: Easy-to-Use, Incorporation of Graphics


### Easy-to-Use Pediatric eDiary


#### Evening Diary


How much did you strain when you pooped?


 0 - no straining

 1 - mild straining

 2 - moderate straining



 3 - severe straining

 4 - very severe straining



#### Evening Diary

You are about to enter information on behalf of the Subject. If this is correct, tap the arrow in the bottom right to continue, or tap the arrow in the bottom left to exit.


 

On the left is an example of a question formulated especially for pediatric subjects. The right exemplifies a screen in the Caregiver Module.

# eCOA Best Practice: Simplified Graphics, Instructions & Feedback

**Child Diary**


Answer each question by thinking only about today. Think about ALL of the time from when you got up this morning, through all of today, until now.



← →

**Child Diary**

Good job! You have answered all of today's questions!  
Remember to answer them again tomorrow morning when you get up.

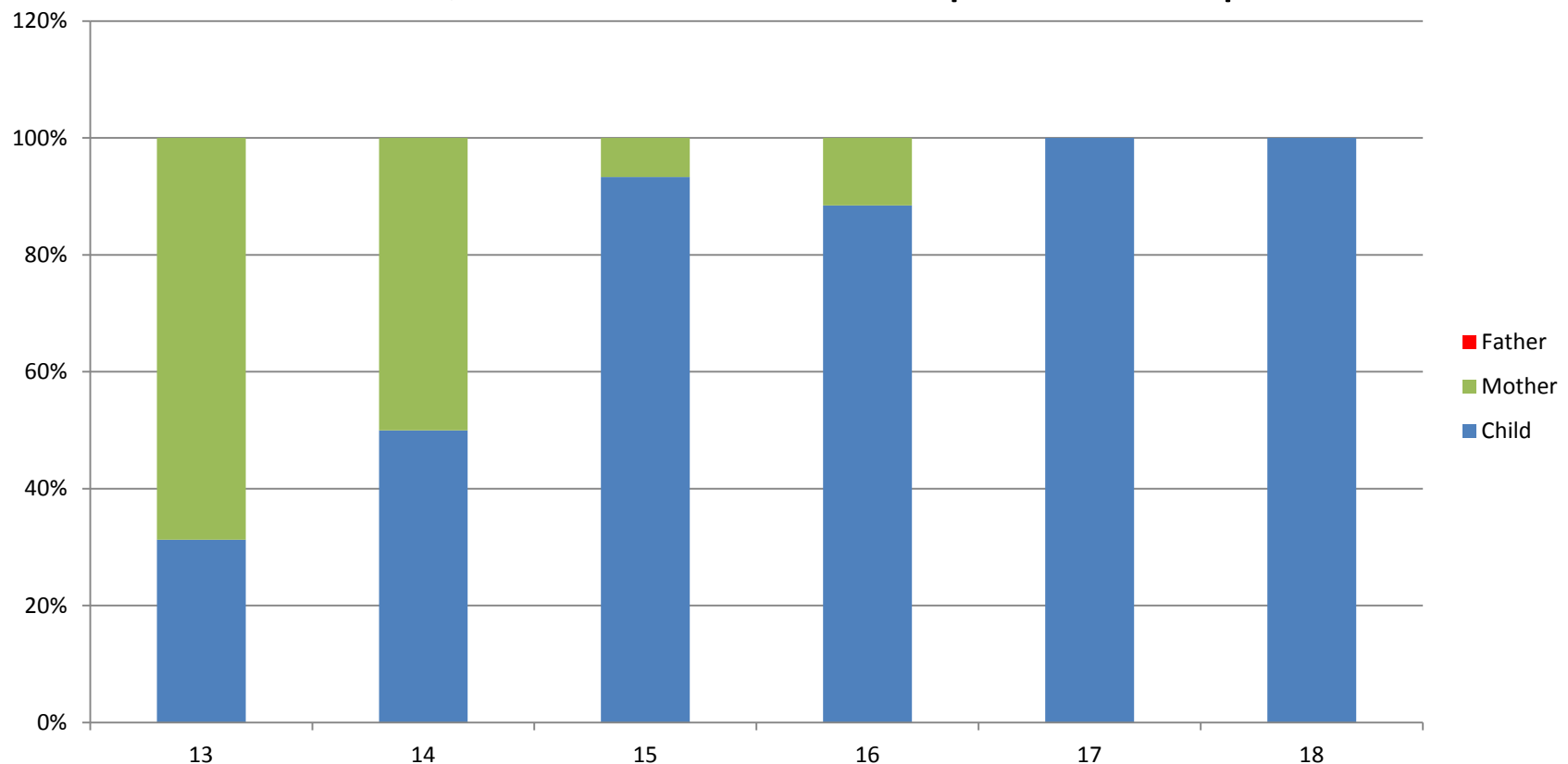


← →

# eCOA Best Practice and the Importance of Age

## Study in Hemophilia (Nr of bleeds, n=155)

- below 12, parents are asked to fill in the diaries
- 13 and above, the choice is left to patients or parents





# eCOA Best Practice: Instructions (1/2)

	Caregiver	Caregiver Initials
<div><div>PHT LogPad B0.23T</div><div>04-Feb-2011 02:01</div><div>Site Number: 1001</div><div>Subject Number: 10011001</div><div>Training Module</div><div>Last Info sent: 04-Feb-2011 01:59</div></div>	<div>If your initials are available from the list, please select them and tap the forward arrow; otherwise tap the New Initials button.</div> <div></div> <div>New Initials</div>	<div>Please enter your initials:</div> <div>A B C</div> <div></div>

# eCOA Best Practice: Instructions (2/2)

**Introduction**

This diary is intended for training purposes: your answers will not be reported.  
It is also intended to provide descriptions of the different types of seizures.  
At the end of the diary, you will be asked to confirm that you understand how to use the device.  
Tap the forward arrow to continue.

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**Definitions 1 / 4**

**PARTIAL** seizures involve only part of the body. They may cause unusual movements or sensations like pins and needles, numbness, tastes or smells.

**ABSENCE** seizures are staring spells.

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**Definitions 2 / 4**

**ATYPICAL ABSENCE** seizures are staring spells with movements like eye blinking or lip smacking.

**MYOCLONIC** seizures are sudden isolated muscle jerks.

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# eCOA Best Practice: Definition of the Caregiver

Definitions 3 / 4	Definitions 4 / 4	Caregiver
<p>CLONIC seizures are repetitive muscle jerks.</p> <p>TONIC-ATONIC seizures are losses of consciousness, stiffenings of the body or losses of muscle tone; the child may fall down.</p>	<p>Primary Generalized Tonic-Clonic seizures (CONVULSIONS) are losses of consciousness, stiffenings of the body followed by jerking movements.</p> <p>OTHER seizures are those which you could not recognize or identify.</p>	<p>This form was filled out by:</p> <p><input type="checkbox"/> Mother</p> <p><input type="checkbox"/> Father</p> <p><input type="checkbox"/> Relative</p> <p><input type="checkbox"/> Caregiver</p>
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## Moderator

- *Linda Abetz-Webb* – Senior Research Director, CEO, Patient-Centered Outcome Assessments

## Presenters

- *Linda Lowes, PhD* – Nationwide Children’s Hospital, Columbus, OH
- *Rob Arbuckle, MA, MSc* – Vice President and Managing Director, Patient-Centered Outcomes, Adelphi Values
- *Valdo Arnera, MD* – Scientific Advisor and General Manager ERT Geneva

## Panelists

- *Laura Lee Johnson, PhD* – Associate Director, Division of Biometrics III, Office of Biostatistics, Office of Translational Sciences, CDER, FDA
- *Andrew E. Mulberg, MD, FAAP, CPI* – Deputy Director, Division Gastroenterology and Inborn Error Products (DGIEP), OND, CDER, FDA
- *Josephine Norquist* – Patient-Reported Outcomes Specialist, Merck Sharp & Dohme, Corp.
- *Anna Rydén, PhD* – Director, Patient Reported Outcomes, AstraZeneca

# Questions?