

**"What Makes Research Findings Useful?:
Listening to Patient's Voices."**

Children's National


Voices of Children in Health Care

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Overview of Comments




- Describe two initiatives in pediatric oncology to solicit and incorporate the ill child's voice in care
- Describe a data-based perspective on the meaning of clinically useful research
 - Is discovering new knowledge sufficient for researchers?*
- Describe challenges to making research clinically useful in pediatric healthcare
 - How is research usefulness related to political will?*




Being Useful: What Does that Mean?

'The purpose of life is not to be happy. It is to be useful, to be honorable, to be compassionate, to have it make a difference that you have lived and lived well.'




Ralph Waldo Emerson

Being Useful: What Does that Mean?

The important thing is that men should have a purpose in life. It should be something useful, something good.

Dalai Lama

How is a researcher useful for a child?

What is the meaning for us and for the child of a researcher being 'useful'?

If we know the meaning of being 'useful' to a child, what are the behaviors that derive from being 'useful' to a child?

Can a child tell us that we are 'useful?' Will we trust the child's guidance and confirmation?



How is a researcher useful to a dying child?

Can we trust the voice of a child who will not recover from his illness or injuries?

Do we have the skills to extract the seriously ill child's voice before that voice is silent?



Child Voice: A Part of the Family Voice



The Child's Voice in Patient-Reported Outcomes

"...any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."

U.S. Department of Health and Human Services, Food and Drug Administration, 2009



Of What Benefit is the Child's Voice?

- Accurate symptom, function and quality of life assessments
- Impact of therapy
- Impact of care
- Patient and parent trust of clinicians and satisfaction with care/Relationship with treatment decision- making



Why seek the child voice in pediatric oncology?

- 36 children are diagnosed with cancer every day/40,000 children receive cancer treatment each year
- Cancer and its treatment has significant burden on children's life
- >60% of children will participate in a clinical trial



Pivotal Point in Measuring the Child Voice in Pediatric Oncology

Recent History of Measuring Child Voice (Pre-PROMIS)

- Symptom, function, quality of life
- Ability of the ill child and the survivor to report
- Willingness of parent to allow child to report
- Occasionally self-report measures are embedded in clinical trials
- Rarely linked to care outcomes or care decisions
- Rarely measuring child voice related to end-of-life care



Pivotal Point in Measuring the Child Voice in Pediatric Oncology

Recent History of Measuring Child Voice

- Cancer-Specific Measures
 - Fatigue Scale – Child
 - Fatigue Scale – Adolescent
 - Fatigue Scale – Parent
 - BASES
 - PedsQL v.3 – Cancer
 - PedsQL – Brain Tumor
 - PNET
 - BARF



A Researcher Being 'Useful' to an Ill Child

Science, my lad, is made up of mistakes, but they are mistakes which it is useful to make, because they lead little by little to the truth.

Jules Verne



Pivotal Point in Measuring the Child Voice in Pediatric Oncology: PROMIS



- Developmental and Measurement (Item Response Theory) Frameworks
- Item banks and computerized adaptive testing (CAT) system
 - qualitative bases (focus groups with children and parents – well, acute and chronic illnesses)
 - Literature review
- Publicly available
- Not disease-specific, broader age range (8 to 17 years of age; 8 to 18 years of age)



Varni, Thissen, Stucky, et al., *Qual Life Res*, 2015; Epub ahead of print
 Quinn, Thissen, Liu, et al. *Health Qual Life Outcomes*, 2014; 12(1): 160.
 Varni, Magnus, Stucky, et al., *Qual Life Res*, 2014; 23(4): 2233-43.



Emotional Distress

Anger
Anxiety
Depression

Physical Functioning

Mobility
Upper Extremity

Pain Interference

Fatigue

Peer Relationships

Asthma Symptoms

In Development:

Experience of Stress
Family Belongingness
Pain Behavior
Pain Intensity
Pain Quality
Physical Activity
Subjective Well Being

www.nihPROMIS.org; <http://www.assessmentcenter.net>

Liu, Hinds, Wang, et al., *Cancer Nursing*, 2013; 36(5): 368-74.



PROMIS Measures in Pediatric Oncology

Feasibility and Acceptability

STUDY	PROMIS I (Cross-Sectional) n = 203	PROMIS II (Longitudinal) n = 96	PROMIS III (Incurable Cancer) n = 20
Refusal Rate	7.5%	12.1%	26%
Enrollment Rate	92.5%	87.9%	74%
Missingness by Measure	0	1.32% (T1) 1.18% (T2) 0.77% (T3)	0 (T1) 1.2% (T2)
Missingness by Item	Not Examined	39.1% - no missingness Not related to sex or age; type of activity	Not Examined

Menard, Hinds, Jacobs, et al., *Cancer Nursing*, 2014; 37(1): 66-74.



PROMIS Measures in Pediatric Oncology

Known Groups Validity

PROMIS I (Cross-Sectional)	Active Treatment n = 93	Survivorship n = 107
Depression	* p = 0.01	
Anxiety	* p = 0.05	
Peer Relationships		* p < .001
Pain Interference	* p = 0.001	
Fatigue	* p < .001	
Upper Extremity		* p < 0.001
Mobility		* p < 0.001

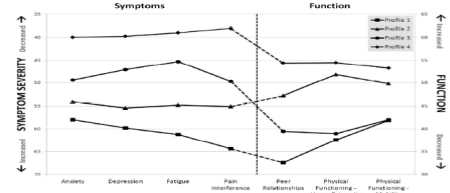


Hinds, Nass, Ruccione, et al., *Pediatr Blood Cancer*, 2013; 60 (3): 402-8.



Child Voice Symptom and Function Data Analysis: No Single Voice

Figure 1. Mean PROMIS Domain Scores of 4 Latent Profiles Generated by LPA for 200 Children with Cancer



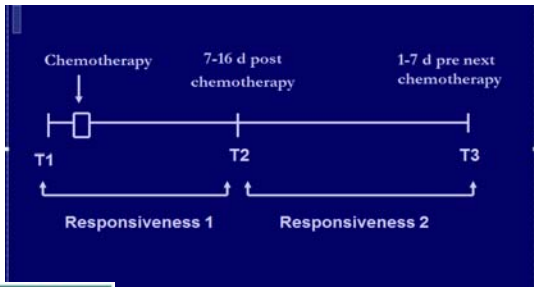
Domain scores are on a T-score metric, normed in the general pediatric population to have a mean of 50 and a standard deviation of 10. PROMIS = Patient Reported Outcomes Measurement Information System, LPA = latent profile analysis.



Backner, Wang, DeWalt, et al., *Pediatr Blood Cancer* 2014; 61 (7): 1282-8.



PROMIS II: Predicted



Child Voice Symptom and Function Data Analysis: Latent Profile Analysis and PROMIS II

Predicted Score Pattern during a course of chemotherapy from child report of *pain, depression, anxiety and fatigue*:

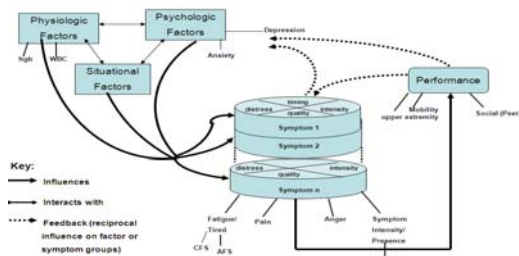
L H L

Actual Score Pattern Outcomes – 3 dominant patterns

H	H	H	(27.5%)
L	L	L	(39.1%)
L	H	H	} (33.4%)
L	L	H	



Validating the Child's Voice: Theoretical Framework for PROMIS I, II, III

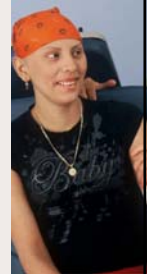


Second Initiative: Child Voice and Treatment Toxicity

The Federal Government mandates all cancer trials report adverse events (AEs)

The standard practice in oncology trials is **clinician grades all AEs** using Common Terminology Criteria for Adverse Events (CTCAE)

- Clinicians underreport the number and severity of symptoms.
- More than 1/3 of the 790 AEs have subjective aspect requiring patient-report to assure validity of AE reporting
- Therefore:** the child's perspectives in grading subjective AEs must be integrated into care.



Second Initiative: Child Voice and Treatment Toxicity

AE reporting is an essential activity in treatment trials

- AEs can result in increased cost due to patient harm and hospitalizations
- Ensures patient safety
- Provide data to sponsors, regulators, patients, and clinicians about treatment effects.

We ask much of ill children including experiencing intrusive, even painful treatments and procedures but we do not systematically ask their feedback about treatment or care impact.



Second Initiative: Child Voice and Treatment Toxicity

Parent and Clinician reports systematically under-report the prevalence and severity of symptomatic AEs.

Study of fatigue in children (7-12 years) with cancer undergoing chemotherapy*:

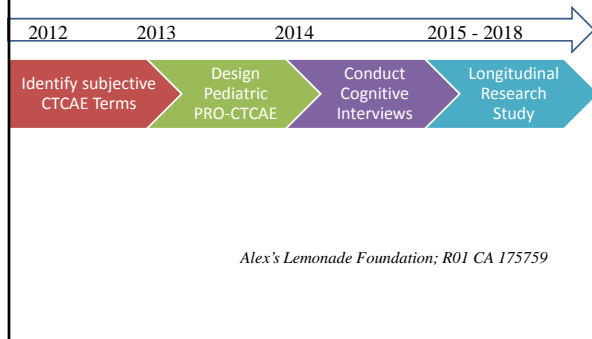
- Child and parent: $r = 0.35$
- Child and clinician: $r = 0.16$

Study with pediatric bone marrow transplant patients, child & clinician association**:

- Pain: $r = .25$
- Fatigue: $r = .23$
- Mental health: $r = .31$



Pediatric PRO-CTCAE Design and Validation Process



Clinician Characteristics (N = 181 invited)

Variable	Survey 1 (N=135)	Survey 2 (N=121)
Professional Degree		
Physician	69 (51%)	61 (51%)
Physician Assistant	4 (3%)	7 (6%)
Nurse Practitioner	31 (23%)	27 (23%)
Registered Nurse	25 (19%)	28 (23%)
Years in Pediatric Oncology		
2-8 years	60 (44%)	46 (38%)
9-15 years	42 (31%)	36 (30%)
16+ years	33 (25%)	39 (32%)
Gender		
Female	99 (73%)	85 (71%)
Children's Oncology Group Site		
Children's Hospital Los Angeles	36 (27%)	33 (27%)
Children's National Medical Center	28 (21%)	30 (25%)
DFCI / Boston Children's Hospital	18 (13%)	14 (12%)
Palmetto Health Children's Hospital	7 (5%)	7 (6%)
St. Jude Children's Hospital	22 (16%)	14 (12%)
University of Minnesota	7 (5%)	9 (7%)
UNC / NC Cancer Hospital	17 (13%)	14 (12%)

16 Core CTCAE terms		
Abdominal Pain	Diarrhea	Nausea
Anorexia	Fatigue	Pain
Anxiety	Fever	Peripheral sensory neuropathy
Constipation	Headache	Vomiting
Cough	Insomnia	
Depression	Mucositis oral	
47 Other selected CTCAE terms		
Abdominal distension	Epistaxis	Restlessness
Alopecia	Fall	Skin ulceration
Arthralgia	Fecal incontinence	Sneezing
Blurred vision	Flashing lights	Sore throat
Bruising	Flatulence	Suicidal Ideation
Chills	General muscle weakness	Tinnitus
Concentration impairment	Hiccups	Urinary frequency
Dizziness	Hoarseness	Urinary incontinence
Dry eye	Hot flashes	Urinary tract pain
Dry mouth	Hyperhidrosis	Urinary urgency
Dry skin	Memory Impairment	Urine discoloration
Dysgeusia	Myalgia	Urticaria
Dyspepsia	Palpitations	Voice alteration
Dysphagia	Photosensitivity	Watering eyes
Dyspnea	Pruritus	Wheezing
Edema limbs	Rash acneiform	

Pediatr Blood Cancer 2013;60:1231-1236

The First Step to Integrating the Child's Voice in Adverse Event Reporting in Oncology Trials: A Content Validation Study Among Pediatric Oncology Clinicians

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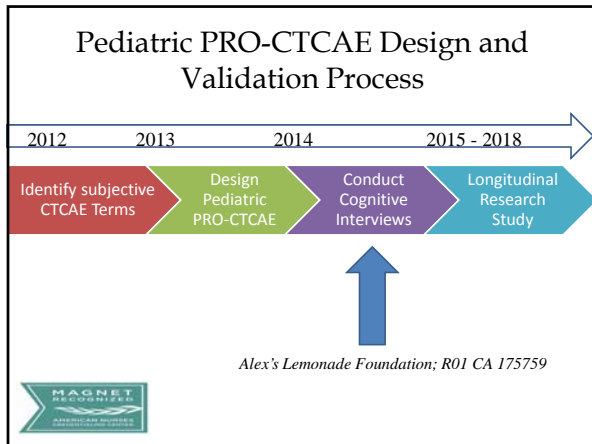
Purpose: Children with cancer experience significant toxicities while undergoing treatment. Documentation of adverse events (AEs) in clinical trials is mandated by federal agencies. Although many AEs are subjective, the current standard is clinician reporting. Our long-term goal is to create and validate a self-report measure of subjective AEs for children aged 7 years and older that will inform AE reporting for the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). This content validation study aimed to identify which of the AEs in the current CTCAE should be included in a pediatric self-report measure. **Methods:** We sought expert panel review and consensus among 187 pediatric clinicians from seven Children's Oncology Group institutions to determine which of the 790 AEs are amenable to child self-report. Two survey iterations were used to identify suitable AEs, and clinician agreement estimated by the content-validity ratio (CVR) was assessed. **Results:** Response rates for surveys 1 and 2 were 72% and 67%, respectively. After the surveys, 64 CTCAE terms met the criteria of being subjective, relevant for use in pediatric cancer trials, and amenable to self-report by a child. The most frequent reasons for removal of CTCAE terms were that they relied on laboratory or clinical measures or were not applicable to children. **Conclusion:** The 64 CTCAE terms will be translated into child-friendly terms as the basis of the child-report toxicity measure. Ultimately, systematic collection of these data will improve care by enhancing the accuracy and completeness of treatment toxicity reports for childhood cancer. **Pediatr Blood Cancer** 2013;60:1231-1236. © 2013 Wiley Periodicals, Inc.

Key words: adverse events; cancer; clinical trials; patient-reported outcomes; pediatric; validity

INTRODUCTION

In the US, cancer will be diagnosed in approximately 12,000 children between the ages of 0 and 14 years during 2012 [1], and more than 60% of children with cancer will participate in clinical trials [2,3]. The federal government mandates that all trials report adverse events (AEs) [4]. The standard lexicon for grading and reporting AEs in oncology clinical trials is the Common Terminology Criteria for Adverse Events (CTCAE) developed by the

ensure that all CTCAE terms relevant for children were included in, and terms without relevance for children excluded from, the development of the pediatric version of the PRO-CTCAE measure. A secondary study aim was to identify "core" subjective AEs that are prevalent in children across a range of cancer (and treatment) types and are therefore of high clinical priority when seeking to measure treatment impact.



Second Initiative: Child Voice and Treatment Toxicity

In-depth one-on-one interviews will evaluate children's and their proxies' comprehension of the PRO-CTCAE questions.

1. What is the most appropriate wording of the question stems?
2. Do children of different age levels interpret symptom terms in the same way?
3. What is the most easily comprehensible response scale?
4. How does the recall period affect responses?

Part I of the Interview Script:

Section A: Discuss recent symptoms with participant

First, I'd like you to tell me how you have been feeling over the past 7 days.

Cognitive Interviewing Strategy

Age Group	Pediatric Form A (x items)	Pediatric Form B (x items)	Pediatric Form C (x items)	Pediatric Form D (x items)	Totals
7-8 years	6 children 6 proxies	6 children 6 proxies	6 children 6 proxies	6 children 6 proxies	48 English speaking children and proxies (24 dyads)
9-12 years	6 children 6 proxies	6 children 6 proxies	6 children 6 proxies	6 children 6 proxies	48 English speaking children and proxies (24 dyads)
Age Group	Adult Form A (x items)	Adult Form B (x items)	Adult Form C (x items)		Totals
13-15 years	8 children 8 proxies	8 children 8 proxies	8 children 8 proxies		48 English speaking youth and proxies (24 dyads)
16-20 years	8 children 8 proxies	8 children 8 proxies	8 children 8 proxies		48 English speaking youth and proxies (24 dyads)

Second Initiative: Child Voice and Treatment Toxicity

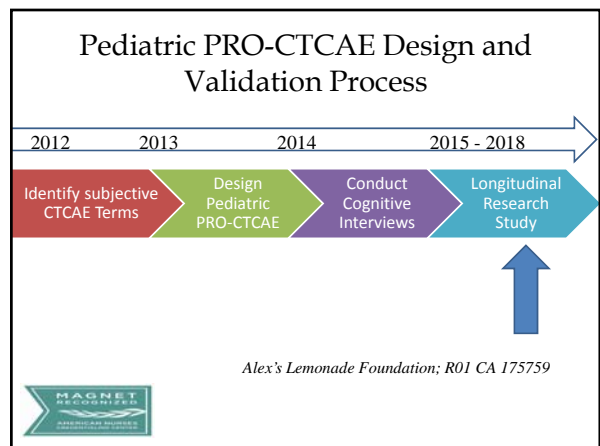
Phase I of Cognitive Interviewing

7 – 8 year olds } Pediatric PRO-CTCAE

9 - 12 year olds }

13 - 15 year olds }

16 – 20 year olds } Adult PRO-CTCAE



How Many Voices? Three Units of Analysis

- Clinician Voice
- Child Voice
- Parent Voice
 - Measuring agreement over time
 - Estimation of change, concern
 - Effect of training to report
 - Family patterns
 - Triadic patterns

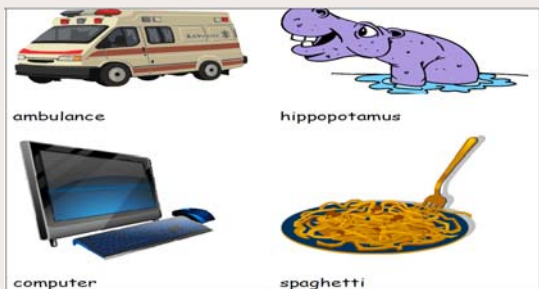


Closing Points

- Children can self-report during illness, end-of-life care and in survivorship
 - PROMIS measures are sensitive to time, group
- Parents and clinicians add important voices to the ill child's treatment and end-of-life experiences
 - Single unit analyses and interpretations (ill child, parent, clinician) are informative but insufficient



What Makes Research Findings Useful for Ill Children?



What Makes Research Findings Useful for Ill Children?

From every study, we can and need to extract trustworthy, easy to grasp information to share with children, families, staff and others.

- 'Do You Know...' information sheets
- 'Research One liners'
- 'Research Moments'



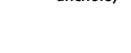
What Makes Research Findings Useful for Ill Children?

- Deliberately seek the child's voice in systematic ways across studies
(become the sensitive instrument that can detect nuance and subtle differences in the responses)
- Seek the child's voice in a way that does not disturb the parental role



What Makes Research Findings Useful for Ill Children?

- Embed the child voice and parent voice measures in all phases of clinical trials and at established points in survivorship
- Explain the importance of honest reporting at the beginning of treatment to the child and parent
 - Study the actual use of the reports in clinical care – does care change?
- Measure child and parent voices consistently at meaningful points during treatment and link the child, parent and clinician reports to traditional endpoints and phenotypes (clinically interpretable anchors)



What Makes Research Findings Useful for Ill Children?

- Assess reports for patterns at the level of child, parent and family
- Develop validity assessments of the child, parent, family reports and patterns and link these to treatment outcomes – trustworthy and actionable voices in treatment and care



What Makes Research Findings Useful for Ill Children?

A life spent making mistakes is not only more honorable, but more useful than a life spent doing nothing.

George Bernard Shaw



Of What Benefit is the Child's Voice?

- Accurate symptom, function and quality of life assessments
- Impact of therapy
- Impact of care
- Patient and parent trust of clinicians and satisfaction with care/Relationship with treatment decision- making



Do We Trust the Ill Child's Voice?

If we do not trust the child's voice, we will not ask.

If we do not trust the child's voice, we will not act on the voice.

If we ask, it is like a promise to the child to listen, to act in respect of the child's voice.



What Makes Research Findings Useful for Ill Children?

'Just ask me. I am the right person for you to be asking these questions because I know all about it.'

15 year old male with relapsed leukemia

'Because it was mainly stuff about myself and I know everything about myself'

9 year old with a solid tumor

