“What Makes Research Findings Useful?: Listening to Patient’s Voices.”

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
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

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
- Publically available
- Not disease-specific, broader age range (8 to 17 years of age; 8 to 18 years of age)

PROMIS Measures in Pediatric Oncology

<table>
<thead>
<tr>
<th>Study</th>
<th>PROMIS II (Cross-Sectional) n = 203</th>
<th>PROMIS II (Longitudinal) n = 96</th>
<th>PROMIS III (Incurable Cancer) n = 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refusal Rate</td>
<td>7.5%</td>
<td>12.1%</td>
<td>26%</td>
</tr>
<tr>
<td>Enrollment Rate</td>
<td>92.5%</td>
<td>87.9%</td>
<td>74%</td>
</tr>
<tr>
<td>Missingness by Measure</td>
<td>0</td>
<td>1.32% (T1)</td>
<td>1.18% (T2)</td>
</tr>
<tr>
<td>Missingness by Item</td>
<td>Not Examined</td>
<td>0</td>
<td>1.32% - no missingness</td>
</tr>
</tbody>
</table>

Emotional Distress
- Anger
- Anxiety
- Depression

Physical Functioning
- Mobility
- Upper Extremity

Pain Interference
- Pain
- Pain Intensity
- Pain Quality
- Physical Activity
- Subjective Well Being

Subjective Well Being

References:

PROMIS Measures in Pediatric Oncology

Known Groups Validity

<table>
<thead>
<tr>
<th>PROMIS I (Cross-Sectional)</th>
<th>Active Treatment n = 93</th>
<th>Survivorship n = 107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>* p = 0.01</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>* p = 0.05</td>
<td></td>
</tr>
<tr>
<td>Peer Relationships</td>
<td>* p &lt; .001</td>
<td></td>
</tr>
<tr>
<td>Pain Interference</td>
<td>* p = 0.001</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>* p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Upper Extremity</td>
<td>* p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>* p &lt; 0.001</td>
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</tbody>
</table>


Child Voice Symptom and Function Data Analysis: No Single Voice

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

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%)

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
- Provides 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.

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 of 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survey 1 (N=135)</th>
<th>Survey 2 (N=121)</th>
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<tbody>
<tr>
<td>Professional Degree</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>69 (51%)</td>
<td>61 (51%)</td>
</tr>
<tr>
<td>Physician Assistant</td>
<td>4 (3%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Nurse Practitioner</td>
<td>31 (23%)</td>
<td>27 (23%)</td>
</tr>
<tr>
<td>Registered Nurse</td>
<td>29 (19%)</td>
<td>28 (23%)</td>
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<table>
<thead>
<tr>
<th>Years in Pediatric Oncology</th>
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</thead>
<tbody>
<tr>
<td>2-5 years</td>
</tr>
<tr>
<td>6-10 years</td>
</tr>
<tr>
<td>10+ years</td>
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<table>
<thead>
<tr>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
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<table>
<thead>
<tr>
<th>Children’s Oncology Group Site</th>
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<tbody>
<tr>
<td>Children’s Hospital Los Angeles</td>
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<tr>
<td>Children’s National Medical Center</td>
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<tr>
<td>DFCI / Boston Children’s Hospital</td>
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<tr>
<td>Palmetto Health Children’s Hospital</td>
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<tr>
<td>St. Jude Children’s Hospital</td>
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<tr>
<td>University of Minnesota</td>
</tr>
<tr>
<td>UNC / NC Cancer Hospital</td>
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<table>
<thead>
<tr>
<th>16 Core CTCAE terms</th>
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<tbody>
<tr>
<td>Abdominal Pain</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Depression</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>47 Other selected CTCAE terms</th>
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</thead>
<tbody>
<tr>
<td>Abdominal distension</td>
</tr>
<tr>
<td>Alopecia</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Blurred vision</td>
</tr>
<tr>
<td>Bruising</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Concentration impairment</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Dry eye</td>
</tr>
<tr>
<td>Dry mouth</td>
</tr>
<tr>
<td>Dry skin</td>
</tr>
<tr>
<td>Dysgeusia</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Dysphagia</td>
</tr>
<tr>
<td>Diplopia</td>
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The First Step to Integrating the Child’s Voice in Adverse Event Reporting in Oncology Trials: A Content Validation Study Among Pediatric Oncology Clinicians
Pediatric PRO-CTCAE Design and Validation Process

2012 2013 2014 2015 - 2018

Identify subjective CTCAE Terms
Design Pediatric PRO-CTCAE
Conduct Cognitive Interviews
Longitudinal Research Study

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

Phase I of Cognitive Interviewing

7 – 8 year olds
9 - 12 year olds
13 - 15 year olds

7 – 8 year olds
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?

- 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

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